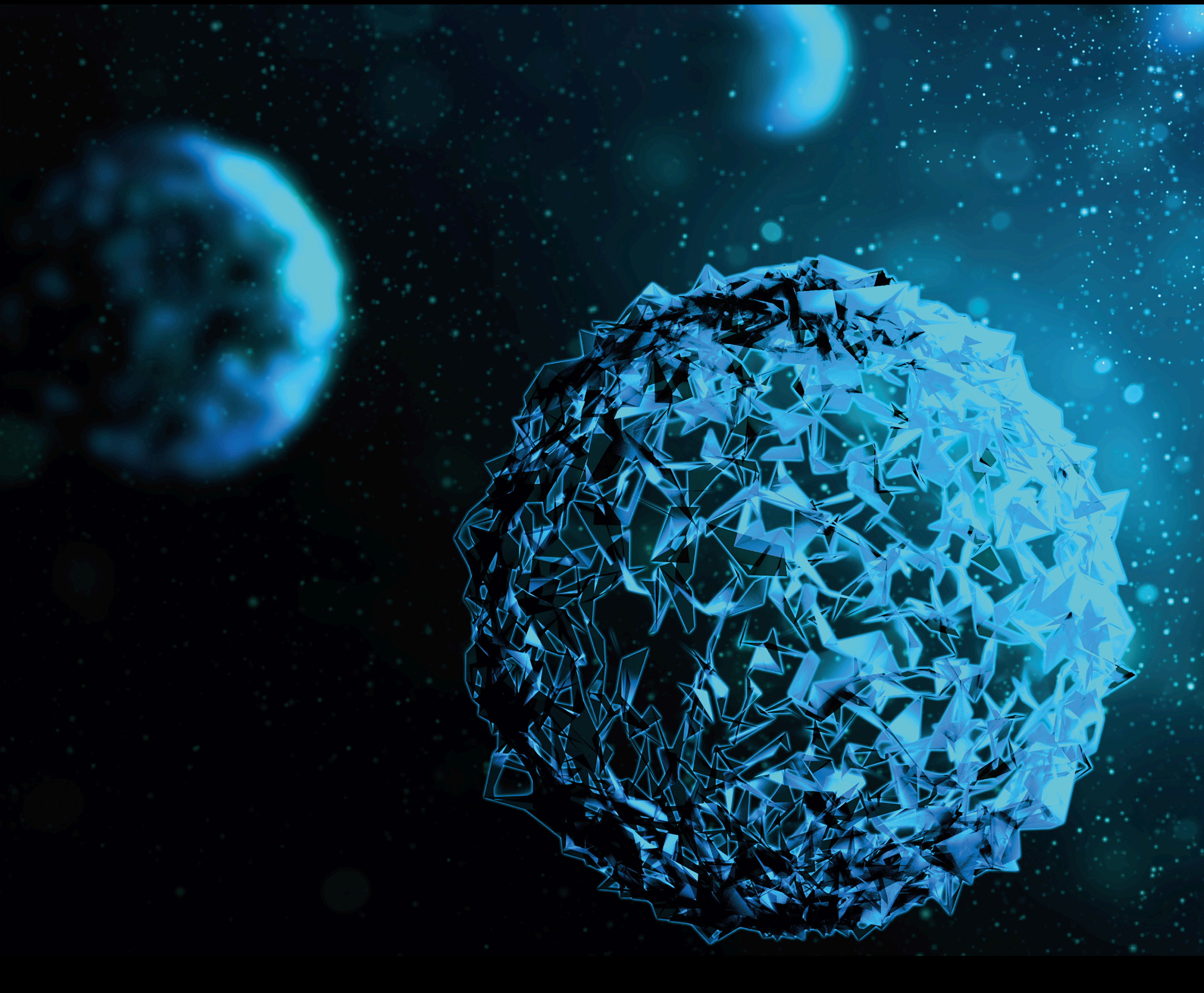
BioMed Research International

Artificial Intelligence Device Development and Applications in Rehabilitation Medicine

Lead Guest Editor: Wen Si
Guest Editors: Lei Jiang, Boya Nugraha, and Lu Zhang



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Retraction

Retracted: Research Progress of Deep Learning in the Diagnosis and Prevention of Stroke

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(5) Incoherent, meaningless and/or irrelevant content included in the article

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The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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Retraction

Retracted: Design and Application of Electronic Rehabilitation Medical Record (ERMR) Sharing Scheme Based on Blockchain Technology

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Retraction

Retracted: Application Experience and Patient Feedback Analysis of 3D Printed AFO with Different Materials: A Random Crossover Study

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Retraction

Retracted: A Retrospective Study on the Efficacy of Two Different Rehabilitation Interventions on KOA: Shock Wave Therapy vs. Electroacupuncture Therapy

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Retraction

Retracted: Handgrip Strength-Related Factors Affecting Health Outcomes in Young Adults: Association with Cardiorespiratory Fitness

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Retraction

Retracted: Urine Albumin/Creatinine Ratio and Microvascular Disease in Elderly Hypertensive Patients without Comorbidities

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Review Article

Poststroke Cognitive Impairment Research Progress on Application of Brain-Computer Interface

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Brain-computer interfaces (BCIs), a new type of rehabilitation technology, pick up nerve cell signals, identify and classify their activities, and convert them into computer-recognized instructions. This technique has been widely used in the rehabilitation of stroke patients in recent years and appears to promote motor function recovery after stroke. At present, the application of BCI in poststroke cognitive impairment is increasing, which is a common complication that also affects the rehabilitation process. This paper reviews the promise and potential drawbacks of using BCI to treat poststroke cognitive impairment, providing a solid theoretical basis for the application of BCI in this area.

1. Introduction

Strokes rank first among long-term disabling diseases [1]. Poststroke cognitive impairment (PSCI) is one of the most common residual symptoms of strokes. In a recent review and meta-analysis of hospital-based studies, PSCI is reported to be 53.4% after stroke. Results from the STROKOG consortium showed different domains of cognitive impairment in 30–35% of patients a short time after a stroke [2]. It not only affects the quality of life of stroke patients but also places a heavy burden on society and the economy. An important feature of PSCI is that it is preventable and treatable [3], so it is important to explore how to improve cognitive function after strokes using modern neurorehabilitation techniques. Brain-computer interface (BCI), as a new rehabilitation technology, not only can be used to evaluate the efficacy of cognitive impairment after strokes [4] but may also be applied to the rehabilitation of cognitive ability. This is of great significance for the early diagnosis and treatment of cognitive impairment after stroke, and for preventing mild cognitive impairment from developing into vascular dementia or other diseases.

2. Overview of PSCI

Poststroke cognitive impairment (PSCI) is one of the major complications of strokes and refers to a series of syndromes from mild cognitive impairment to dementia caused by strokes [5]. PSCI is common in all stroke subtypes, and even patients with transient ischemic attacks (TIA) are at risk of developing cognitive impairments and dementia [6]. PSCI can affect multiple cognitive domains, including executive functioning, memory, attention, language, and visuospatial abilities [7], although executive dysfunction and memory impairment are the most common [8]. Recent studies have found that within a year after stroke occurrence, as many as 53.4% of patients could show cognitive impairments [9], and the proportion of mild cognitive impairment could be as high as 80%. Additionally, more than 7% of PSCI patients could develop dementia [10].

The type of stroke lesions, reperfusion status, brain compliance, and nutritional status of stroke patients are all related to the rehabilitation of stroke-related cognitive impairment [11]. Additionally, in recent years, functional neuroimaging studies have found that cognitive impairment after stroke is also associated with lesions in distal brain regions and changes in brain network connectivity [12]. Dacosta-Aguayo et al. used the resting-state functional magnetic resonance imaging (RS-fMRI) technology to study these phenomena and found that PSCI patients had reduced functional connectivity [13]. Another large study of heterogeneous stroke patients also found that damage to certain brain regions may lead to disturbances in brain networks and a variety of cognitive symptoms [14]. Through neuroimaging studies, Jaywant et al. found that poststroke executive dysfunction was related to changes in resting-state functional connectivity. Overconnectivity of the cognitive control network and reduced connectivity of the transhemispheric frontal and parietal networks were closely related to poststroke executive function. Therefore, cognitive training that targets brain networks is also helpful for treating executive dysfunction following stroke [15]. In addition, nonverbal cognitive impairment in patients with aphasia after stroke has been shown to be associated with extensive destruction of white matter microstructure integrity, wherein uncinate fascicle (UF) damage is closely related to spatial perception (SP) and motor practice (MP) deficits [16].

PSCI evaluation usually employs neuropsychological tests such as the Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE). However, these scales usually rely on subjective judgment and do not contain domain-specific cognitive assessment information (i.e., they do not measure reading or writing abilities). As a result, test results may not be accurate for PSCI patients [17]. Additionally, there is no effective treatment strategy for PSCI-related cognitive decline. Currently, drug therapy and rehabilitation therapy are the main clinical treatments for PSCI. The purpose of drug therapy is mainly to control the risk factors related to cerebrovascular disease, to improve the main symptoms of cognitive impairment and accompanying mental symptoms such as depression and anxiety, and to delay the progression of the disease [18]. However, there are many side effects associated with drug therapy. Acupuncture has also been used as a complementary and alternative therapy for patients who do not respond well to drug therapy [19]. Acupuncture can also improve the cognitive functioning of patients with poststroke cognitive impairment but no dementia (PSCIND) and reduce the chance of developing PSD [20].

Rehabilitation treatment mainly involves cognitive rehabilitation, including relearning previously learned knowledge or gaining new knowledge—which causes functional changes and enhances cognitive functioning. Cognitive rehabilitation mainly includes traditional cognitive retraining and cognitive enhancement with the application of high-tech equipment. Noninvasive brain stimulation (NIBS) has been used for the treatment of PSCI, but the selection of stimulation site, stimulation parameters, and mechanisms need further study [21]. In addition, adaptive conjunctive cognitive training (ACCT) also has positive effects on PSCI patients' attention and spatial awareness and reduces depression symptoms [22]. Finally, artificial intelligence, including neurocognitive robots [23], and computer-assisted cognitive training have also been employed to improve cognitive impairment in stroke patients [24]. Current cognitive rehabilitation treatments are often only used for defects in cognitive field training, and PSCI patients tend to show higher rates of cognitive defects. Further, the patient's mental health also plays a role in reducing cognitive impairment [25], so multimodal assessment and rehabilitation should be used for PSCI patients. As an emerging technology, BCI uses brain neural activity as input, employs mathematical algorithms to decode neural signals, and converts intentions or decisions into commands for external machines such as computers. These computers can then be used to monitor subjects' mental state or to improve cognitive abilities. In recent years, BCI has been employed to treat a variety of neurological diseases. Further, researchers have applied different BCI schemes to improve PSCI, which is of great importance for treating PSCI-related cognitive impairments, and for the prevention of vascular dementia and other diseases.

3. Overview of BCI

3.1. Development of BCI. As early as 1969, Rosenfeld et al. [26] detected modulated visual and auditory responses in animals. Later, inspired by the adjustable nature of brain activity, Professor Vidal from the University of California, Los Angeles, created BCI to realize a technology for reading brain signals [27] and first proposed the idea of using operant conditioning to control computers. It was not until 1977 that Pfurtscheller and Aranibar found through experiments that subjects could change the frequency band power of EEG alpha (8-12 Hz) and beta (12-25 Hz) signals in the motor region of the brain by moving or imaginatively moving certain body parts and that changes would occur both at the beginning of movement and during the migration process. This marked the formation of the first human biofeedback BCI [28].

3.2. Construction of BCI System. In contrast to the conventional brain information output pathway, BCI is a new communication and control system that connects the brain or nervous system to any device capable of processing or computing. BCI can be controlled by various signals sent by the brain. These electrical, magnetic, or metabolic activity signals can then be further amplified, filtered, decoded, and translated into signals to control external devices. A complete BCI system usually consists of signal acquisition, signal processing, feature extraction and selection, signal classification, external control, and user feedback. Each of these parts has a variety of developed methods, and a heterogeneous combination of different approaches allows the BCI to be customized to meet specific disease needs (Figure 1).

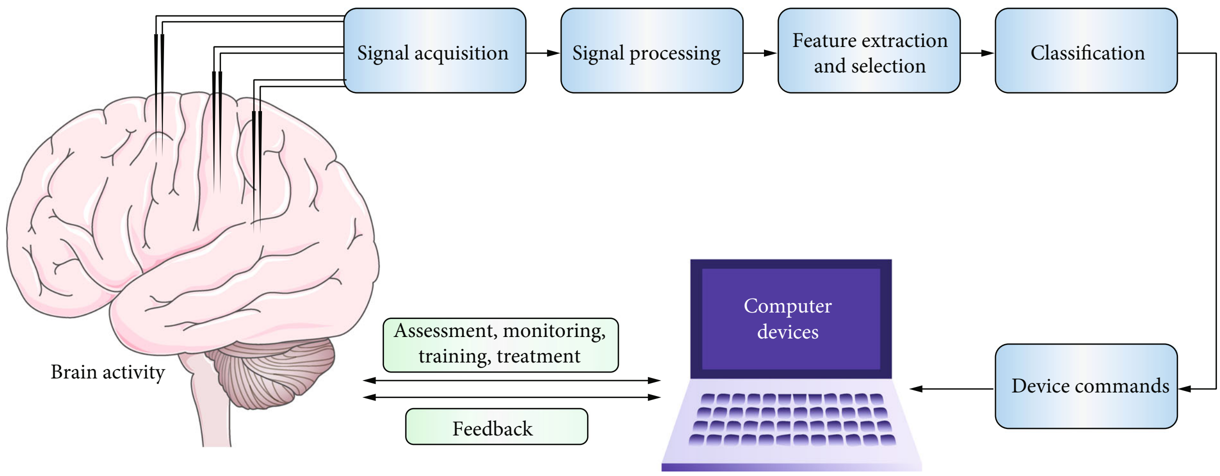

FIGURE 1: Basic layout and process of a BCI system.

3.2.1. Signal Acquisition and Processing. BCI can be divided into two types—noninvasive and invasive—depending on signal acquisition mode. Noninvasive BCI is a safer, more convenient, and noninvasive technique to obtain human brain signals directly from the scalp. Among noninvasive BCIs, EEG is the most commonly used signal acquisition method. These BCI systems are divided into exogenous BCI and endogenous BCI according to the source of EEG stimulation. Exogenous BCI refers to EEG signal patterns induced by external stimuli, such as event-related potentials (ERPs) [29], auditory steady-state responses (ASSR) [30], steady-state visual evoked potentials (SSVEPs), and P300 [31]. Hwang et al. introduced a novel BCI mode based on ERP-BCI for patients with complex eye dysfunction, which does not rely on gaze function and can complete visual stimulation under closed eyes [32]. Hill et al. are developing new BCI systems to make previously employed ASSR stimulations more natural and intuitive [33]. Jiang et al. developed new BCI systems based on EEG of the event-related potential-neurofeedback-brain-computer interface (ERP-NF-BCI) platform used for training. During the training process, subjects' brain electrical signals were captured using a wireless EEG headset. At any given time, subjects were instructed to direct their attention to tasks related to a stimulus or to ignore an irrelevant stimulus. Patients trained the EPR-NF-BCI system to provide positive feedback and improve target visual stimulus attention abilities [34]. Among all of these systems, BCI based on P300 is the most popular because it has high classification accuracy and a fast information transfer rate (ITR). In addition, the hold-release function developed by Alcaide-Aguirre et al. allows for faster (6-16 times) and more continuous control of P300-BCI [35], and changes in patients' visual and auditory senses affect its performance [36]. However, when SSVEP-BC-based visual stimulation is applied in elderly patients, eye fatigue is common, and epileptic seizures are sometimes induced. Another BCI system is based on the endogenous BCI paradigm, which uses self-modulating EEG signal patterns without external stimulation, such as sensorimotor rhythms (SMRs) [37], slow cortical potentials (SCPs) [38], and signals generated by imagining motor movements without the need for actual muscle movement.

Magnetoencephalography (MEG) has many advantages over electroencephalography, such as its ability to record gamma signals from the cortical sulcus and from higher wavelengths. However, MEG is rarely applied because it needs to use expensive superconducting materials [39]. Functional magnetic resonance imaging (fMRI) can also reflect the activity of neurons by measuring blood flow signals. Sulzer et al. found that subjects were able to control blood oxygenation level-dependent (BOLD) signals in specific brain regions and that the BOLD signals were related to low and high-frequency field potentials in BCIs [40]. However, real-time fMRI has poor temporal resolution and a high price, so it is not applicable to BCIs. Functional near-infrared spectroscopy (FNIRS), by contrast, is cheaper and more portable. However, the signal-to-noise ratio (SNR) and spatiotemporal resolution of FNIRS are also limited, and the communication rate is even lower than that of EEG-based BCI [41]. For invasive signals, signals on the pia mater surface (also known as electrocorticogram (ECoG)), signals on the dura mater surface (epidural field potentials (EFPs)), or signals in the cortex (sharp waves or local field potentials (LFPs)) are usually used [42]. For example, Vansteensel et al. designed an ECoG-BCI-based cortical intracortical brain-computer interface (IBCI) for typing and playing games [43]. Moses et al. used a high-density cortical electrogram to realize real-time decoding of the superior temporal gyrus during an auditory exercise [44]. Research by Pandarinath et al. further showed that IBCI could provide high communication rates [45]. In addition, biofeedback BCIs based on LFPs may also be able to obtain more reliable neural signals for corresponding regulation [46]. Compared with noninvasive signals, invasive signals have a higher SNR, higher communication rate, and higher temporal and spatial resolution. In order to improve BCI performance, a series of problems must be overcome—including low classification accuracy, small degrees of freedom, and a steep learning curve for understanding how to operate BCI. Hybrid brain-computer interfaces (hBCIs) and multimode BCIs have been developed for rehabilitation that attempt to solve these problems—including P300 and SSVEP, P300 and motor imagery (MI), EEG and eye movement (EOG), EEG and electromyography (EMG), and EEG and electrocardiogram (ECG) setups [47]. For example, Fazli et al. [48] developed a multimodal BCI that combined EEG and near-infrared spectroscopy (NIRS) and improved the signal classification accuracy for 90% of participants. In addition, Wang and Jung also proposed a collaborative BCI that integrates information from multiple users. Compared with single-user BCIs, this system effectively integrates the brain activities of a group of people, which vastly improves the overall performance [49]. Multimodal BCI has high sensitivity and specificity and is resistant to ambient noise. The era started with noninvasive brain-computer interfaces (BCIs), based on electroencephalography (EEG) [50]. Noninvasive BCI systems have one advantage over the invasive methods, as they do not require any surgical intervention, and their implementation is neither difficult nor risky [51]. Their nature of being noninvasive has made this technique popular. The application potential is vast and ranges from clinical to home-entertainment applications, such as the popular and inexpensive customer-grade EEG headsets [52]. There is still a drive toward a more cost-effective, smaller, portable, and efficient device in medicine especially in the neuroscience field [53, 54]. The future direction also involves a combination of noninvasive BCIs, coupled with augmented reality (AR) systems. Future trends in the development of the BCI systems are probably strongly correlated with the development of intelligent algorithms for the analysis of biomedical data and the systems with a reduced number of channels [55]. Therefore, noninvasive BCIs and hBCIs based on EEG show the most promise for application in neurological rehabilitation (Table 1).

3.2.2. Feature Extraction and Feature Classification. Frequency bands recorded by EEG can be identified and used to express the patient's intention after signal transformation and classification. Therefore, effective extraction of EEG signal characteristics and accurate classification are two of the important steps for any BCI system. Kober et al. used an EEG Fast-Fourier Transform (FFT) feature extraction method to detect the effects of neurofeedback (NF) training on memory improvement following stroke [56]. Ieracitano et al. used the continuous wavelet transform (CWT) to develop a new automatic classification method of EEG records based on multimodal machine learning for the detection of patients with mild cognitive impairment (MCI) or Alzheimer's disease (AD) [57]. Based on P300-BCI, Onishi and Natsume improved the linear discriminant analysis (LDA) feature classifier into an integrated stepwise linear discriminant analysis (SWLDA) classifier with overlapping partitions, which significantly improved BCI performance [58]. Chen et al. [59] proposed a BCI based on the SSVEP innovative coding method, which uses a relatively large frequency flicker (10, 12, and 15 Hz) stimulation of brightness, and low-frequency alternating (0.5, 1 Hz) color modulation, to induce intermodulation frequencies at the same time. This increases the number of single frequency flashes and allows the system to have a classification accuracy rate of 93.83% and ITR of 33.90 bits/minute. Some new EEG feature extraction and classification have also recently emerged. For example, the sparse Bayesian learning [60] has been used to predict the behavior or cognitive state of subjects. Deep learning algorithms [61] are also used to extract multi-source EEG signals and carry out high-precision classification. In addition, the use of complex networks is a new method which can be used to analyze the structural changes of brain networks in patients with nervous system diseases and to reveal the relationship between brain functional patterns and disease progression. In addition, the Granger causality methods are also used to evaluate brain connectivity [62]. These newly optimized feature extraction and classification methods continue to improve BCI performance, which provides a good technical foundation for the rehabilitation of cognitive impairment after stroke.

3.2.3. External Control and User Feedback. External control involves the processing of collected signals into digital commands using a combination of filtering, transformation, and classification algorithms, and then receipt of those signals by effectors. Any device that can be programmed to receive functional commands can be used in the rehabilitation of cognitive impairment after stroke. However, fully functional BCI systems provide feedback only online to the user after the effectors receive instructions. Feedback methods include visual, auditory, and tactile sources, among which visual feedback is most common [63]. There is also neurofeedback (NF), which is a special form of feedback based on EEG-BCI. During NF, the application interface displays brain activity intuitively and in real time to the user. The user can then self-regulate brain functioning according to the feedback and make it return to a normal state. NF techniques are usually based on EEG or RT-fMRI. NF training based on EEG signals involves repeated tasks and has been shown to improve attention, executive function, and memory [64]. Robineau et al. showed that, in six stroke patients, RT-fMRI-based NF improved visual stimulation awareness [65]. In addition, NF training can also regulate sensory motor rhythm (SMR) in stroke patients and healthy elderly people and is associated with significant improvements in behavior and memory during nonverbal learning tasks [66]. In addition, some BCI systems synchronize neural activity with feedback devices to create closed-loop multimodal feedback, enhance the Hebbian plasticity, and help restore motor function. Further, closed-loop BCI systems can also be used as biofeedback platforms to improve and enhance individual cognitive ability. New settings, including multiplayer collaboration and EEG-NF in virtual environments and videogames, are also constantly being developed in order to make BCI more powerful, exciting, and challenging [67].

3.3. The Mechanism of BCI Promoting Cognitive Rehabilitation after Stroke

3.3.1. Promote Neural Remodeling. The human brain performs complex cognitive functions such as learning, memory, and emotion processing through the normal activity of nerve cells. When the body's normal neural pathways are

Table 1: Comparative analysis of various methods used for recording features.

Risky		Signal source	Advantages	Disadvantages	Frequency of utilization	Description
Noninvasive	EEG	EEG signals	Cheap; high time resolution; portable	Low spatial resolution; longer training time; easily disturbed	Commonly used method	Measuring electrical signals produced by the human brain
		Spontaneous signals	Without external stimulus	Longer training time	Commonly used method	No external stimulus produced the signal
		Evoked signals (P300)	Price acceptable; training time short	Long time attention; easy to fatigue	Commonly used method	EEG signals are generated when stimulated by a flash of light/a latency of 250-500 ms
		Evoked signals (SSVEP)				EEG signals are generated when stimulated by looking at a frequency of flickering
		MEG	High spatial resolution; training time short; easy to record	Expensive; poor portability	Rarely used method	Record magnetoencephalogram signals generated by the human brain
		fMRI	High spatial resolution	Expensive; limited position; unportable low time resolution; unsuitable for real-time BCI; restricted to bold signals	Infrequently used method	Record the signals generated by brain metabolism
		fNIRS	Price affordable; high spatial resolution; unnecessary use precise parameter setting; portable	Low time resolution;	Infrequently used method	Record the signals generated by brain metabolism
		PET	Real time	Relatively high prices; complexity of the accompanying infrastructure	Only used in research and clinical neurology	Noninvasive measurement of cerebral blood flow, metabolism, and receptor binding in the brain
Invasive		ECoG	No training; high SNR; higher spatial resolution	Time consuming; easy induce epilepsy	Rarely used method	Electrodes are placed under the skull to measure electrical activity
		LFPs	High temporal and spatial resolution; high SNR	Easy lose signals	Rarely used method	Electrodes are placed under the skull to measure electrical activity

injured, BCI can serve as part of the injury "bypass." BCI connected directly to an external control device, or BCI used in tandem with other techniques (i.e., functional electrical stimulation (FES) and virtual reality (VR)), has been shown to promote functional recovery [68–70]. Nie and Yang showed that MI promoted functional neuron remodeling, increased the expression of scaffold proteins and regulatory proteins, enhanced synaptic plasticity, and promoted learning and memory-related cognitive functions [71]. Ortiz et al. also confirmed that a new type of BCI based on gamma bands could enhance neuroplasticity, promote cognitive and motor rehabilitation, improve the operating accuracy of exoskeleton control, and improve attention levels during gait walking [72]. Kleih et al. also proposed that BCI could enhance the plasticity of neurons by activating language circuits and thus promote the recovery of language functions in patients with aphasia after stroke [73]. fMRI and diffusion tensor imaging further confirmed the neuroplasticity of stroke patients after BCI therapy [74]. On this basis, Zuo et al. [75] proposed a hybrid BCI system that involves both MI and P300. In this program, 12 healthy subjects were asked to imagine writing Chinese characters in a specific order. Results showed that the recognition accuracy of patients exposed to mixed BCI was significantly higher than that of those exposed to single P300 ($P < 0.05$) or MI ($P < 0.01$) BCI alone.

3.3.2. Promote Neural Network Recovery and Enhance Brain Connectivity. Changes in brain network connectivity patterns are highly predictive of cognitive performance. Cassidy and Cramer have argued that all cognitive rehabilitation-related neuronal remodeling phenomena are related to changes in brain network structures [76]. Fodor et al. used 128-channel EEG to study event-related synchronic potentials (ERS) in 17 patients with mild cognitive impairment (MCI) and 21 healthy controls during the Sternberg working memory task and found that event-related synchronic (ERS) potentials in α and β bands were significantly reduced in patients with MCI, indicating early impairment of neural networks related to working memory [77]. Toppi et al. also estimated the brain connectivity of patients with memory deficiencies after stroke based on the EG-BCI-NF training method and found that improvement of memory function was associated with increases in the predensity index of brain connectivity and the left temporal alpha band, indicating that memory improvements are related to brain network functioning [78]. Taken together, all of these studies provide strong evidence for the utility of BCI for clinical treatment. Zhang et al. also found changes in brain connectivity related to the use of a motor imagination brain-computer interface (MI-BCI) in the field of poststroke rehabilitation. The results showed that right ventral internal parietal sulcus degree centrality (DC), left parietal lobe eigenvector centrality (EC) and cortical thickness (CT), and right dorsolateral prefrontal cortex CT were significantly correlated with MI-BCI. In addition, analysis of subjects' working characteristics and machine learning classification found that the EC and CT could effectively predict the low intelligent users from the high intelligent users with an accuracy of 83.3%, indicating that BCI based on brain connectivity can also be used for cognitive assessments [79].

4. Application of BCI in PSCI

BCI was first used in stroke rehabilitation treatment in 2009 [80].BCI can not only detect brain activity—it can also be used for cognitive assessment and training for patients with cognitive impairment, help patients express their intentions, address cognitive and memory impairments, and promote communication. BCI technology has broad development prospects for improving cognitive functioning, patient autonomy, and quality of life. The range of applications of BCI in PSCI is shown in Table 2.

Table 2 contains a total of 16 articles, of which 2 articles are on BCI assessment, 4 articles focus on the training of cognitive function by BCI, and 8 articles about the treatment of cognitive impairment by BCI. Park et al. [82] used BCI to assess cognitive engagement after stroke, while Shukin et al. [90] used BCI to evaluate the efficacy of poststroke rehabilitation training with BCI. Through different methods of BCI cognitive training [81, 83, 85, 91], there are significant improvements in multiple domains of cognitive impairment, including executive ability [83, 89], language ability [84], attention [87, 92], visuospatial ability [91, 93], and memory [85, 94–96]. One of the other two articles showed that mental fatigue state influenced the assessment and performance of BCI [88], while the others showed that brain-computer interface rehabilitation training was ineffective in patients after stroke. See the application below for specific analysis.

4.1. Assessment of BCI for PSCI. With the development of new intelligent rehabilitation technologies, BCI systems can also provide more objective and accurate neuropsychological assessments for PSCI patients. Zhang et al. designed a cognitive functioning system for MCI screening using BCI technology. The results from the new functional assessment system were highly correlated with the traditional Montreal cognitive assessment system ($r = 0.83$) [79].

Park et al. used EEG to evaluate the cognitive engagement of 11 patients with chronic stroke while performing motor tasks and observed that active motor tasks induced greater event-related desynchronization (ERD) in the bilateral motor cortices and supplementary motor area (SMA) than did passive motor tasks [82]. In addition, Lyukmanov et al. used a BCI-based system to conduct neuropsychological tests on 55 patients with motor disorders after their first stroke who were undergoing rehabilitation training. The Fugl-Meyer assessment (FMA) and action research arm test (ARAT) were used to detect the severity of motor impairment and arm paralysis after stroke in the control group. The BCI group received BCI-based neuropsychological tests and motor imagination training that incorporated exoskeleton feedback under the control of BCI. At the end of the evaluation, both groups showed improvements in ARAT and FMA (parts A-D, H, and I), but only the BCI group showed improvements in ARAT's grasp score ($P = 0.012$), pinch score ($P = 0.012$), gross movement score ($P = 0.002$). Certain neuropsychological tests (i.e., the Taylor figure test,

TABLE 2: Summary of articles on BCI-based applications for poststroke cognitive impairment.

Publications	Title	Signals	Sample	Tasks	Positive?
Yan et al. [81]	*Cognitive Alterations in Motor Imagery Process after Left Hemispheric Ischemic Stroke*	Event-related potential (ERP), event-related synchronization (ERD/ERS), P200, P300	11 ischemic stroke patients	Motor imagery (MI) training	Yes (cortical activation was altered differently in each cognitive substage of motor imagery)
Park et al. [82]	*Assessment of Cognitive Engagement in Stroke Patients from Single-Trial EEG during Motor Rehabilitation*	Electroencephalography (EEG); ERD	11 chronic stroke patients	Cognitive function assessment	Yes
Toppi et al. [78]	*Investigating the Effects of a Sensorimotor Rhythm-Based BCI Training on the Cortical Activity Elicited by Mental Imagery*	Sensorimotor (SMR)	2 hemisphere stroke patients	10 sessions SMR-based brain-computer interface-(BCI-) NF training	A: yes (spatial attention and memory) B: no
Cho et al. [64]	*The Effect of Neurofeedback on a Brain Wave and Visual Perception in Stroke: A Randomized Control Trial*	Electroencephalography (EEG)	27 stroke patients	Neurofeedback (NFB) training	Yes (concentration and visual perception)
Pichiorri et al. [83]	*Brain-Computer Interface Boosts Motor Imagery Practice during Stroke Recovery*	High-density electroencephalographic (EEG)	28 subacute stroke patients	BCI-supported-MI training	Yes (FMA score ($P < 0.03$). EEG sensorimotor power spectra occurred with greater involvement of the ipsilesional hemisphere in response to MI of the paralyzed trained hand)
Kober et al. [56]	*Specific Effects of EEG-Based Neurofeedback Training on Memory Functions in Poststroke Victims*	SMR, upper alpha	17 stroke patients	EEG-based neurofeedback training	70%: yes (verbal short- and long-term memory)
Reichert et al. [66]	*Shutting Down Sensorimotor Interferences after Stroke: A Proof-of-Principle SMR Neurofeedback Study*	Multichannel electroencephalography (EEG), sensorimotor rhythm (SMR)	1 stroke patient	10 sessions Sensorimotor rhythm (SMR) neurofeedback training	Yes (short- and long-term memory)
Kleih et al. [84]	*Toward a P300-Based Brain-Computer Interface for Aphasia Rehabilitation after Stroke: Presentation of Theoretical Considerations and a Pilot Feasibility Study*	P300, EPR	5 stroke patients	Visual-P300-based BCI spelling training	Yes (attention, accuracy in spelling, and reading)
Kober et al. [85]	*Upper Alpha-Based Neurofeedback Training in Chronic Stroke: Brain Plasticity Processes and Cognitive Effects*	Multichannel electroencephalogram (EEG)	2 chronic stroke patients	Upper alpha-based neurofeedback training	Yes (memory functions)
Tonin et al. [86]	*Behavioral and Cortical Effects during Attention-Driven Brain-Computer Interface Operations in Spatial Neglect: A Feasibility Case Study*	EEG	3 stroke patients	Covert visuospatial attention- (CVSA-) driven BCI training	Yes (visuospatial)
Lyukmanov et al. [82]	*Poststroke Rehabilitation Training with a Brain-Computer Interface: A Clinical and Neuropsychological Study*	Electroencephalography (EEG)	55 hemiplegic stroke patients	12 sessions BCI-supported mental training	Yes (the Taylor figure test, choice reaction test, head test, and online accuracy rate)

Table 2: Continued.

Publications	Title	Signals	Sample	Tasks	Positive?
Shukin et al. [4]	*Poststroke Rehabilitation Training with a Brain-Computer Interface: A Clinical and Neuropsychological Study*	P300-evoked potentials	140 chronic cerebral ischemia patients	Neuropsychological testing	Yes
Kotov et al. [87]	*Usage of Brain-Computer Interface + Exoskeleton Technology as a Part of Complex Multimodal Stimulation in the Rehabilitation of Patients with Stroke*	Multimodal stimulation	44 stroke patients	Neural interface brain-computer + exoskeleton (BCI) training	Yes (memory, attention, visual, and constructive skills)
Foong et al. [88]	*Assessment of the Efficacy of EEG-Based MI-BCI with Visual Feedback and EEG Correlates of Mental Fatigue for Upper-Limb Stroke Rehabilitation*	EEG	11 stroke patients	EEG-based MI-BCI visual feedback training	Yes (fatigue-monitoring)
Chung et al. [89]	*Therapeutic Effects of Brain-Computer Interface-Controlled Functional Electrical Stimulation Training on Balance and Gait Performance for Stroke: A Pilot Randomized Controlled Trial*	Sensorimotor rhythm (SMR), midbeta, and theta	25chronic hemiparetic stroke patients	BCI-controlled functional electrical stimulation (BCI-FES) feedback training	Yes (executive capacity: gait velocity and cadence ($P = 0.020$), step length ($P = 0.031$))
Sebastián-Romagosa et al. [70]	*Brain-Computer Interface Treatment for Motor Rehabilitation of Upper Extremity of Stroke Patients—A Feasibility Study*	Electroencephalography signals	51 stroke patients	25 sessions MI-BCI training	No

choice response test, and head test) were significantly correlated with online accuracy. These results suggest that increasing the level of BCI control in exoskeleton-assisted physical therapy can significantly improve rehabilitation effects after stroke [97]. At the same time, BCI can also monitor the global attention level related to task processes, and monitoring the changes in attention during BCI training can ensure better focus on the current task [98].

BCI can also be used to evaluate efficacy. Shukin et al. [90] used cognitive P300-evoked potentials and a diagnostic scale to evaluate treatment dynamics in patients with cognitive impairment of chronic cerebral ischemia. Patients with chronic cerebral ischemia aged were divided into a treatment group and a control group and were treated with cytoflavin and methyl succinate hydroxypyridine, respectively. During the treatment period, the neurophysiological parameters of both groups improved, especially in the patients treated with cytoflavin. The amplitude of P300 in the left hemisphere was 9.21 (8.36, 10.11)~12.41 (10.23, 13.37) μV, which was a 1.3-fold increase. The right hemisphere amplitude was 6.48 (5.26, 7.35) to 11.04 (9.29, 12.18) μV, a 1.7-fold increase.

BCI can also be used to monitor physiological changes in stroke patients. J Wilson et al. [99] reported that a platform based on BCI COSBID-M3 multimode monitoring for stroke and other neurological diseases could monitor cortical functioning and pathology in real time during surgeries. In summary, BCI has been widely applied to assess cognitive functioning, but the single mode BCI also has some drawbacks, including unreliable data, long length of assessments, and fatigue. Therefore, the application of multimodal BCI and modified BCI for multiple cognitive tests may be more effective for comprehensive clinical assessments.

4.2. Training of BCI for PSCI. The application of BCI training for the rehabilitation of limb motor function after stroke is developing rapidly. Cognitive training is another focus of neurorehabilitation research. Kruse et al. conducted a meta-analysis on the influence of BCI training on the recovery of brain function in patients with strokes and concluded that BCI training could enhance recovery [100]. Lee et al. have also shown that BCI training can improve attention, visuospatial abilities, and memory in older adults. They are also developing a larger BCI cognitive training intervention trial for the cognitive assessment of patients with early dementia [101].

Neurofeedback training (NFT) and motor imagination (MI) training are two common methods of BCI cognitive function training. Cho et al. [91] found that NFT showed a significant increase in attention and visual perception over traditional rehabilitation training. They also showed significant changes in EEG-detected beta values, indicating that NFT can actually improve cognitive performance. BCI devices also can monitor NFT influences on memory function. One example is the work of Silvia Erika Kober, on memory defects in stroke patients. Before NFT, EEGs showed that the left brain artery ischemic stroke patients' hemispheres had pathological delta (0.5-4 Hz) and highest alpha (10-12 Hz) frequencies. After NFT, the EEG showed more standard frequency topography on both sides. Memory tests on patients with bilateral subarachnoid hemorrhage revealed significant improvement in both short-term and long-term memory and slight improvement in working memory, following NFT. Patients with left cerebral artery ischemic strokes had significant improvements in long-term memory after NFT [85]. Ruiz et al. [102] found that conscious control of the anterior insula increased cognitive flexibility in a facial emotion recognition task in healthy elderly people through real-time BCI-NFT, further demonstrating the effectiveness of BCI in cognitive enhancement and training.

Gomez-Pilar et al. [103] showed that NFT based on MI-BCI could enhance cognitive function in elderly patients. In this study, 63 subjects were recruited—31 in the NFT group and 32 in a control group that did not receive training. Subjects were asked to practice five tasks of increasing difficulty over and over again before giving neural feedback through a motion visual-controlled, moving-on-screen program. Cognitive test results showed that, after five NFT sessions, four measures of cognitive function (visuospatial, language, memory, and intelligence) improved significantly ($P < 0.01$). Thus, repeated BCI training may promote neural plasticity by repeatedly stimulating the parts of the brain involved in cognitive processing. In addition, studies have shown that MI can promote neural plasticity [104]. Yan et al. [81] used EEG to study 11 patients with left hemisphere ischemic cerebral apoplexy and found that, after MI training, cognitive changes occurred. MI training has been widely used to promote functional rehabilitation after stroke. In addition, BCI can provide real-time, quantitative monitoring of brain function in conjunction with MI training. Pichiorri et al. [83] studied 28 patients with subacute severe cerebral apoplexy dyskinesia and used BCI to support MI training. They found that, compared with patients who underwent unsupported MI training, the BCI training upper-limb Fugl-Meyer assessments improved significantly ($P < 0.03$), sensorimotor alpha and beta bands were more highly synchronized, and resting ipsilateral brain connectivity within the same bands increased significantly ($P < 0.05$).

BCI training is also affected by language, gender, and other conditions. BCI versions and language settings may also be different. However, even when employed in patients who speak different languages, there appear to be no significant differences in BCI effectiveness. Lee et al. [105] used EEG-based BCI in 32 English-speaking and 39 Chinese-speaking elderly patients and found that cognitive abilities were improved in both groups. However, gender has a moderating effect on BCI. For example, Yeo et al. [106] applied a BRAINMEM training system to improve cognitive functions, such as attention, working memory, and delayed recall in the elderly, and found that there was no significant difference in overall cognitive performance between the training group and the nontraining group after treatment. In men, however, the intervention group performed better than the control group ($P = 0.046$).

4.3. *Treatment of PSCI by BCI.*

The treatment of PSCI by BCI mainly manifests in improved executive function, attention, memory, language, and visuospatial abilities.

4.3.1. *Executive Function.*

Due to executive dysfunction after stroke, patients may be uncoordinated and/or experience judgment errors while driving. However, BCI may remedy these problems [107]. Chung et al. used brain-computer interface-controlled functional electrical stimulation (BCI-FES) rehabilitation techniques in patients with chronic hemiplegic stroke and found that the training significantly approved their ability to walk after stroke and that these differences were also significantly increased compared to patients who experienced FES rehabilitation only [89].

4.3.2. *Memory Function.*

Memory is a cortical function that preserves information and past experiences and helps people acquire new skills and learn new information. Memory can also be divided into short-term and long-term memory. Due to severe functional damages and memory loss in stroke patients, early memory deficit intervention may help prevent the disease from progressing to Alzheimer's disease or vascular dementia [108].

BCI technology has been shown to improve memory, attention, and consciousness in older people with cognitive impairments. Lee et al. [109] used EEG-BCI in 31 healthy elderly patients and measured cognitive improvements using cognitive ability tests, card matching games, and other memory and attention tasks. The results showed significant improvements in immediate memory ($P = 0.038$), delayed memory ($P < 0.001$), and concentration ($P = 0.039$) scores. In addition, NF therapy based on EEG can also regulate the brain activity of stroke patients and help restore memory functions. Reichert et al. [94] applied NFT to basilar artery thrombosis stroke patients and found that sensorimotor rhythm neurofeedback (SMR-NF) training positively affected memory functioning. Prior to starting NFT, patients presented with short- and long-term memory deficits ($T - \text{scores} < 40$). After SMR-NF, the performance of various memory functions was better than expected.

Toppi et al. [95] studied the effects of a BCI closed-loop neurofeedback intervention scheme. Two stroke patients (patient A, female, 70 years, right hemisphere stroke lesion; and patient B, male, 20 years old, left hemisphere stroke) underwent 10 sessions of SMR-NF training to attempt to address memory impairments. Neuropsychological tests showed that, after NF training, one of the patients' performance accuracy on the Sternberg memory task was significantly increased and reaction time was significantly decreased ($P < 0.05$). Auditory memory and visuospatial short-term memory impairments were also significantly improved after training ($P < 0.05$). Finally, the Rey auditory verbal learning test (RAVLT) and Corsi block tapping test

(CBTT) equivalent scores increased from 1 to 3 and 4, respectively. In addition, in an attempt to enhance memory function, Burke et al. [110] used intracranial electroencephalography (iEEG) in neurosurgery patients to detect θ wave and α wave oscillations associated with optimal memory encoding. They aimed to trigger the occurrence of relevant memory encoding waveforms during the process of recall. This was the first time that iEEG was used to enhance episodic memory in BCI. Kober et al. [96] studied the SMR of 17 stroke patients (11 experienced 12 to 15 Hz and 6 experienced upper alpha frequencies of 10-12 Hz). Results demonstrated that patients in the SMR group showed improvements in short-term memory performance, and working memory performance improved in patients in the upper frequency group. Thus, the effects of NFT in stroke patients were better than those of traditional cognitive training.

4.3.3. Attention. Attention is the core component of cognitive ability. Inattention damages memory and behavioral performances. Most cognitive training therefore seeks to improve attention abilities. Attention is controlled by a network of interconnected cortical regions, including the frontal visual field, the parietal area, some subcortical structures, the superior colliculus, and oculomotor muscles [111]. The frontal cortex region, which plays a key role in attentional control, can be detected by EEG or LFPs as an attention marker due to synchronous neuronal activity [112]. Using EEG-NF-BCI, which measures neural signals and is used to enhance attention and cognitive performance, patients can observe a graphical representation of their brain activity, which is also self-regulated by computer processing into an optimal state. This method has been used to treat a variety of neuropsychological disorders, including PSCI [92]. Foong et al. [88] conducted EEG-based MI-BCI in 11 stroke patients (mean age 55.2 ± 11.0 years) using visual feedback and found significant changes in β-power and EEG signals in frontal and central brain regions when fatigue occurred during the test, indicating that mental fatigue may affect BCI performance to a certain extent. In addition, BCI rehabilitation requires the ability to focus on screens for a long time, so cognitive impairments such as attention deficits in stroke patients may also have an impact on BCI performance. For example, in the P300-BCI system, decreased attention levels and the high working memory loads can result in the ERP signal within the P300 system having low amplitude and long latency period. However, in the nonvisual BCI mode that is based on P300, increases in P300 amplitude may indicate the improvement of attention after training [113]. In recent years, because of new developments in brain imaging and BCI technology, real-time fMRI closed-loop training has successfully improved visual attention and behavioral performance [114]. Thus, while BCI can improve attention, the degree of attention can also affect the performance of BCI.

4.3.4. Language Ability. Another important application of BCI in the recovery of cognitive function is the rehabilitation of speech ability in stroke patients. Flowers et al. reported that more than 30% of all stroke survivors are affected by speech impediments [115]. Compared with stroke patients without aphasia, poststroke aphasia (PSA) patients tend to have more extensive and severe nonverbal cognitive impairments. Among these patients, patients with nonfluent aphasia tend to have more severe disorientation and spatial perception impairments than patients with fluent aphasia [116]. Nolfe et al. [117] suggested that P300 may predict aphasia recovery, and studies have found that the amplitude of P300 decreases in aphasia patients. On this basis, Kleih [84] used the P300-BCI spelling system to assess language functioning in patients with poststroke aphasia. The experiment included five patients with aphasia after stroke. The researchers applied EEG-P300, and ERP during spelling and reading practice, and found that four patients with aphasia after stroke who were initially unable to use the visual P300 could successfully communicate using the P300-based BCI speller with 100% accuracy. One patient who was dyslexic following a stroke was able to read 14-letter words, up from 9-letter words, after BCI training. In addition, the accuracy of spelling and reading improved when attention was focused. The P300 amplitude and attention performance test (German: Testbatterie zur Aufmerksamkeitsprüfung (TAP)) was improved after training in two patients with aphasia after stroke, suggesting that the visual P300-BCI spelling system could be used for language training and could be used to judge cognitive abilities after stroke. However, unlike English words, Chinese characters are usually written with two-dimensional structures. Thus, Han et al. [118] developed a novel Chinese character writing robot controlled by BCI, which used the mixed features of P300 and SSVEP to effectively encode a large instruction set, decode the combined features using take related component analysis, and generate efficient writing of both Chinese characters and English letters. The average accuracy was 87.23%, and the maximum accuracy was 100%. The corresponding information transmission rates were 56.85 bit/min and 71.10 bit/min, respectively. In addition, BCI can also identify EEG signals sent through the BCI and then transmit them to the corresponding receptive brain region as new incoming information. Thus, BCI can facilitate two-way dialogue between two people who cannot communicate [119, 120]. All these factors suggest promise for the application of BCI to improve language abilities in stroke patients.

4.3.5. Visuospatial Ability. BCI can also be used to improve visuospatial abilities. Tonin et al. [86] have shown that BCI can improve laterally dominant attentional visuospatial deficits. By using covert visual spatial attention- (CVSA-) BCI in three patients with left spatial neglect (SN) stroke, they found that the patients could control CVSA-BCI with accuracy rates above 50%. Behavioral RTs were also decreased in two patients ($P < 0.01$). Further, the α-peak loss ratio was significantly decreased ($P < 0.01$), and the asymmetry between hemispheres in the parietooccipital region showed significant improvements ($P < 0.05$). In stroke patients, FC between the right hemispheres was significantly increased, suggesting that CVSA-BCI may help enhance neuroplasticity, reduce the imbalance between hemispheres, increase the connectivity between hemispheres, improve attention, and remedy visuospatial defects.

The BCI multimodal analysis can also predict the cognitive processing depth of visual imagination, memory, language, and other task domains [93]. Hreha et al. [121] followed 1439 stroke patients and used a regression model to observe the relationship between visual acuity and changes in cognitive function. They found that overall visual acuity was associated with a significant decrease in baseline cognitive function. Further, visual impairment (VI) was not associated with rates of cognitive decline.

Kotov et al. [87] studied the effects of multimode BCI stimulation on cognitive function recovery in patients with strokes. A total of 44 patients were examined and treated between 2 months and 2 years after stroke. After treatment, memory, attention, and visual spatial abilities of patients in the treatment group showed significant improvements compared with those in the control group. Thus, multimode and multichannel BCI may help activate neural plasticity, improve the relationship between hemispheres, and promote the recovery of cognitive function in patients with stroke.

In conclusion, BCI has been shown to have many positive effects on PSCI patients, but its long-term efficacy may need to be further verified. It is also worth noting that some studies have shown that BCI is ineffective in improving PSCI. Sebastián-Romagosa et al. [70] recruited 51 stroke patients with upper-limb hemiplegia for 25 rounds of MI-BCI treatment. The Stroop color-word test (SCWT) and MCA were used to evaluate cognitive function before and after treatment, and there were no significant differences in memory and thinking scores, or scores on a self-reported questionnaire.

5. Safety and Stability of BCI

5.1. Signal Security. Sebastián-Romagosa et al. [70] tested the safety and availability of the BCI system in healthy elderly people using a memory training game. They reported no adverse events in any participants during any of the sessions. Immediate memory ($P = 0.038$), visuospatial/structure ($P = 0.014$), attention ($P = 0.039$), and delayed memory ($P < 0.001$) scores were significantly improved. Another BCI training designed to improve cognitive performance found that 10 participants (30.3%) reported a total of 16 adverse events, but all of them were "mild" (except for 1 "moderate" adverse event [105]). Overall, security and usability measures are high, and no serious adverse events have been reported when BCI is used in stroke rehabilitation. However, common treatment-related side effects such as transient nausea, fatigue, and headache may occur. Therefore, there is still a long way to go before BCI technology can really be applied on a large scale.

5.2. Signal Stability. Due to different BCI signal sources, BCI signal stability differs, but it can also be used to evaluate signal stability. Any information gathered in the first few hours of a single unit spike is considered erratic. Multiunit spikes (MSPs) are more stable and last longer than single unit peaks. Bionic BCIs that use MSPs can provide stable performance for about 6 months without recalibration, while bionic BCIs using LFPs remain stable for over a year [122]. Another study showed that MSP-BCI performance remained stable for up to 22 months in one monkey but was only stable for several weeks in another monkey [123], which may also point to individual heterogeneity in BCI application.

Milekovic et al. [124] found that LFP-BCI communication in a brainstem stroke-induced lockout syndrome and in a quadriplegic patients who had amyotrophic lateral sclerosis (ALS) was stable for 76 and 138 days without recalibration, respectively. BCI spelling rates of 3.07 and 6.88 correct characters per minute allow participants to type and write emails. Patients with locked-in syndrome can communicate daily using LFP-BCI without the need for intervention by a technician or caregiver. Quadriplegic patients were treated with repeated intracortical BCI for up to four and a half months. The method uses local field potentials (LFPs), which are more stable than neuronal action potentials, to decode the commands of the participants.

Natural environmental factors also have an impact on BCI signal stability. İşcan and Nikulin [125] examined many factors (i.e., psychology, speech, and audio interference) that might influence signal stability and the ability of patients to finish designated tasks. The experiment involved four conditions: the control group (which had no interference), the speaking group (who were instructed to loudly count from one to ten), the thinking group (who counted from one to ten in their head), and the listening group (who listened to someone else counting from one to ten). The results showed that the average classification accuracy for the speech and thinking groups decreased slightly, while the average classification accuracy of the hearing and the control group was not significantly different. The results indicated that decreases in BCI performance were related to changes in EEG signal quality and increased cognitive load, suggesting signal stability depends on many factors.

6. Difficulties and Challenges

There are several difficulties in the application of BCI in PSCI: (1) improving signal processing algorithms, exploring neural active patterns, quickly and accurately identifying task-related EEG signals, and eliminating interfering EEG signals are the most challenging tasks for the application of BCI systems in stroke-related cognitive impairment. (2) BCI needs to be adaptive to gender-based differences, needs to avoid differences in EEG signals, and needs to be calibrated to subject-specific needs. (3) The efficiency of BCI needs to be improved. (4) The development of a noninvasive, low-cost, easy-to-install BCI system suitable for stroke patients is also critical. In conclusion, BCI technology appears to enhance existing treatments for cognitive impairment after stroke. At present, BCI technology is developing rapidly, but there is still a long way to go before BCI is more widely applied.

7. Summary and Prospects

Cognitive decline after stroke is a major problem. Up to 30% of patients may develop dementia within three months after the occurrence of a cerebrovascular event. If TIA can be applied early and timely, then intervention against cognitive decline in stroke patients can be implemented, and patient prognosis can be improved. The application of BCI technology in poststroke cognitive impairment is a new direction for neurorehabilitation and has already been used in the assessment, training, rehabilitation, and treatment of PSCI. Studies have shown that the BCI can help improve PSCI. BCI can identify neuronal activity, classify and extract information, decode the subjects' intention, through NF and MI and repeated training, promote interneuronal interactions, change synapse potentials, improve brain compliance, improve brain network functional connectivity, adjust the balance between the hemispheres, promote neural plasticity-induced cortical reorganization, and improve cognitive function. Although BCI has shown some improvements for PSCI patients, more studies need to be carried out. Most current studies mainly focus on small samples and short-term observations of efficacy, and there is still a lack of large-scale randomized controlled trials that could verify its effectiveness and long-term efficacy. In addition, animal models cannot fully reflect the complexity of human cognition, which makes the project more challenging. However, with the continuous maturity of modern medical equipment and other technologies, and the application of hybrid BCI that combines multiple modes, BCI will become an even more practical and powerful way to treat PSCI in the future.

Data Availability

This article is a review article and does not contain relevant data.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Xiaowei Sun and Mingyue Li are co-first authors.

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Retraction

Retracted: A Retrospective Study on the Efficacy of Two Different Rehabilitation Interventions on KOA: Shock Wave Therapy vs. Electroacupuncture Therapy

BioMed Research International

Received 8 January 2024; Accepted 8 January 2024; Published 9 January 2024

This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

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(5) Incoherent, meaningless and/or irrelevant content included in the article

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[1] Y. Zhao, X. Wang, and D. Zhang, "A Retrospective Study on the Efficacy of Two Different Rehabilitation Interventions on KOA: Shock Wave Therapy vs. Electroacupuncture Therapy," *BioMed Research International*, vol. 2021, Article ID 2099653, 6 pages, 2021.

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Research Article

A Retrospective Study on the Efficacy of Two Different Rehabilitation Interventions on KOA: Shock Wave Therapy vs. Electroacupuncture Therapy

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Objective. In this paper, we retrospectively reviewed the difference in clinical effectiveness of shock wave therapy and electroacupuncture therapy on knee osteoarthritis. *Methods*. A total of 128 treatment cases of knee osteoarthritis patients were extracted from the medical record system of Shenzhen Longhua District Central Hospital during the period from January 1, 2018, to January 30, 2020. The cases were divided into three groups for different treatments: shock wave group ($n = 54$), electroacupuncture group ($n = 41$), and control group ($n = 33$). The shock wave group was given shock wave therapy combined basis clinical treatment; meanwhile, the electroacupuncture group was given electroacupuncture on the basis of actual clinical treatment. The control group was given conventional topical nonsteroidal anti-inflammatory drugs (Voltaren). Osteoarthritis index scale, NRS scale, and WHOQOL-BREF were observed before treatment, after 2 weeks, and 4 weeks after treatment. *Results*. This study found that the osteoarthritis index scale and NRS scale of the shock wave group and the electroacupuncture group were lower than those before treatment; it had significant difference ($P < 0.001$). In WHOQOL-BREF, the shock wave group and the electroacupuncture group improved significantly four weeks after treatment ($P < 0.001$), which was statistically different from the conventional group ($P = 0.04$). *Conclusion*. Physical and rehabilitation medicine treatment (shock wave therapy) and traditional medical treatment (electroacupuncture) have better clinical effects on knee osteoarthritis, compared with conventional treatment. Shock wave and electric acupuncture have no apparent adverse reaction, suggesting that the treatment is safe and effective.

1. Background and Aim

Knee osteoarthritis (KOA) is a common chronic disease of osteoarthritis, with a relatively high incidence in the elderly. KOA can cause severe systemic physical symptoms such as joint pain, swelling, stiffness, and restricted mobility [1]. The number of patients with KOA worldwide is currently estimated to be as high as 350 million [2]. The prevalence of knee osteoarthritis is 8.1% in China [3]. KOA has become a serious public health problem that seriously affects the life and health of middle-aged and elderly people. Therefore, effective treatment of KOA has become a hot and difficult issue. Traditional Chinese acupuncture has a long history in the treatment of knee osteoarthritis. It has significant effects in relieving patients' pain and improving clinical symptoms, and even in repairing degenerative knee joints with simple, convenient, and easy operation [4–6]. Electroacupuncture (EA) is a form of acupuncture therapy that combines traditional acupuncture with electrical stimulation, which is famous for quantification and repeatability. Previous studies have confirmed the good therapeutic effect of electroacupuncture on KOA. The specific mechanisms include anti-inflammatory, improving blood circulation, and analgesia [7, 8]. In clinical biological research, Gang et al. [9]. found that electroacupuncture can improve the muscle tone of the rectus femoris in KOA patients, and Han and Sun [10] found that electroacupuncture can also improve the gait function of KOA patients. Traditional Chinese medicine can restore the mechanical balance of the knee joint to achieve a therapeutic effect by treating tendons or treating both muscles and bones at the same time. In addition to the direct improvement of muscle function, electroacupuncture also has a complex central analgesic mechanism. At the same time, electroacupuncture not only plays a direct role in improving muscle function but also has a complex central analgesic mechanism [11], which may play a direct anti-inflammatory effect on articular cartilage, resulting to treating pain and alleviating the degradation of KOA cartilage finally [12]. It has been proved that electroacupuncture can improve the atrophy of the rectus femoris and biceps femoris in KOA rabbit models. In addition, electroacupuncture had a protective effect on the articular cartilage of the rabbit KOA model. In recent years, some new methods of noninvasive treatment, such as extracorporeal shock wave, have emerged. Some studies have shown that the mechanism of pain improvement is that shock wave can incapacitate sensory unmyelinated fibers and reduce the expression of nociceptors on neurocutaneous calcitonin gene-related multiskin, thus reducing the pain sensitivity of patients [13]. When the shock wave acts on the local area, it causes minor trauma to the affected area, thus improving the blood supply to the local microcirculation. The levels of interleukin-1, tumor necrosis factor a, and nitric oxide in cartilage were decreased, while the subchondral bone mineral density was increased after extracorporeal shock wave intervention, which were proved that extracorporeal shock wave was beneficial in reducing cartilage inflammation and enhancing subchondral bone strength. The purpose of this study was to analyze the clinical efficacy, adverse reactions, and safety of rehabilitation therapy (shock wave therapy) and alternative medicine (traditional Chinese acupuncture electroacupuncture) in the treatment of knee osteoarthritis. This study provided a new idea of integrated rehabilitation medicine for the clinical treatment of knee osteoarthritis.

2. Method

2.1. Subjects. This study retrospectively selected patients with knee osteoarthritis in the outpatient clinic from January 1, 2018, to December 30, 2020, and followed the necessary inclusion and exclusion criteria. Each participant signed an informed consent form before participation. This study approved by the Ethics Committee of the Central Hospital of Longhua District was conducted by the Central Hospital of Longhua District, Shenzhen.

Diagnostic criteria: defined the criteria for the diagnosis of knee osteoarthritis in 1995 by the American College of Rheumatology [14].

Inclusion criteria: (a) according to the Chinese "Guidelines for the Diagnosis and Treatment of Osteoarthritis," the research subjects who can be clearly diagnosed as knee osteoarthritis; (b) the patients are all over 18 years old; (c) no other treatments have been used for the treatment of osteoarthritis in the past month; (d) informed consent was signed by the recruited patient.

Exclusion criteria: (a) patients with other serious bone and joint diseases, or diseases with similar clinical symptoms; (b) patients who have not signed the informed consent.

The included knee osteoarthritis patients were divided into the shock wave group ($n = 54$), electroacupuncture group ($n = 41$), and control group ($n = 33$) based on different treatments. In this study, the percentage of females is 47.1% and males 52.9% in the control group (mean age 55.84 ± 5.62 years; mean course of disease 4.35 ± 1.23 years); the percentage of females is 51.2% and males 48.8% in the electroacupuncture group (mean age 56.32 ± 5.78 years; mean course of disease 4.82 ± 1.57 years); the percentage of females is 48.1% and males 51.9% in the shock wave group (mean age 55.31 ± 5.54 years; mean course of disease 4.59 ± 1.49 years). The difference in basic population specificity was not statistically significant among the three groups. Please see Table 1.

2.2. Intervention. Each patient with knee osteoarthritis was treated for four weeks.

(1) Shockwave group: shockwave treatment was performed on the basis of Voltaren topical treatment, once every 7 days, the frequency was 7 Hz, and there are 2000 hits each time. Extracorporeal shock wave therapy instrument (Brand: Swiss EMS, Model: Swiss DolorClast Classic)

(2) Electroacupuncture group: electroacupuncture was performed on the basis of Voltaren topical therapy. Specific treatment method: use disposable 40 mm * 0.3 mm sterile acupuncture needles (Universal brand), select the affected side (Liangqiu ST34, Xuehai SP10), (Heding EX-LE2, Zusanli ST36), (EX-LE4) External calf nose ST35), (Yinlingquan SP9, Yanglingquan GB34) 4 sets of electroacupuncture, frequency 1 Hz, time 20 minutes, continuous wave, the size is subject to personal tolerance, and treatment is performed every other day (electroacupuncture instrument, Brand: Shantou Dajia, Model: 6805-AII)

(3) Control group: Voltaren topical treatment. Manufacturer: Beijing Novartis Pharmaceutical Co., Ltd. Appropriate amount for external use, three times a day

Primary endpoints: The Western Ontario and McMaster Universities Osteoarthritis Index, WOMAC.

Secondary endpoints: NRS and WHOQOL-BREF.

2.3. Evaluation. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). (1) The Osteoarthritis Index Score Scale includes three dimensions: pain, stiffness, and difficulty in daily activities, and 24 survey items with a score of 0-96. The pain dimension in the scale contains 5 research survey items, the stiffness dimension in the scale contains 2 research survey items, and the difficulty of daily activities contains 17 research survey items. Each survey item has a score of 0-4. The higher the score, the more severe the disease, showing a positive correlation trend. (2) The Numerical Rating Scale (NRS) is used to evaluate the degree of pain in patients with knee osteoarthritis, and the score ranges from 0 to 10 points. In this clinical study, the patients themselves scored according to the degree of pain. The

Table 1: Baseline data for the three general population groups.

Indicators	Control group ($n = 33$)	Electroacupuncture group ($n = 41$)	Shock wave group ($n = 54$)
Age (year)	55.84 (5.62)	56.32 (5.78)	55.31 (5.54)
Sex n (%)			
m	17 (52.9)	20 (48.8)	28 (51.9)
f	16 (47.1)	21 (51.2)	26 (48.1)
Course of disease (year)	4.35 (1.23)	4.82 (1.57)	4.59 (1.49)

higher the score, the more severe the knee osteoarthritis pain. See Table 2 for details.

(3) Use the World Health Organization's Quality of Life Scale (WHOQOL-BREF) for scoring. Perform clinical evaluation based on changes in points. There are 26 questions in the scale, including 4 fields, namely, the physiological field, the psychological field, the social field, and the environmental field. The scale can generate scores in 4 fields, and field scores are recorded in a positive direction. The higher the score, the better the quality of life. The field score is obtained by calculating the average score of the item it belongs to and multiplying by 4. Physiological domain $(PHYS) = 4 \times [(6 - Q3) + (6 - Q4) + Q10 + Q15 + Q16 + Q17 + Q18]/7$. Psychological domain $(PSYCH) = 4 \times [Q5 + Q6 + Q7 + Q11 + Q19 + (6 - Q26)]/6$. Social domain $(SOCIL) = 4 \times (Q20 + Q21 + Q22)/3$, and environmental domain $(ENVIR) = 4 \times (Q8 + Q9 + Q12 + Q13 + Q14 + Q23 + Q24 + Q25)/8$.

2.4. Statistical Analysis. Statistical analysis was performed using SPSS software 22.0. Quantitative data such as age (years), course of disease (years), osteoarthritis index score, and NRS were all described by statistics. Age, course of disease, osteoarthritis index score NRS, and WHOQOL-BREF score were statistically analyzed by one-way ANOVA LSD (satisfying the effect of homogeneity of variance) and T3 test (not satisfying the effect of homogeneity of variance). Differences were tested using pairwise q-tests. Repeated measurement analysis of variance is used to evaluate the trend of osteoarthritis index score and NRS score with the time of TCM treatment. $P < 0.05$ was considered as statistically significant.

3. Results

3.1. Osteoarthritis Index Score Analysis before and after Treatment. The knee osteoarthritis patients in the control group, the electroacupuncture group, and the shock wave group were scored on the osteoarthritis index before treatment, after 2 weeks of treatment, and after 4 weeks of treatment. There were no statistically significant differences in the total scores of pain and stiffness, daily activities, and osteoarthritis index scores before treatment. After 2 weeks of treatment and 4 weeks of treatment, the total scores of pain, stiffness, daily activities, and osteoarthritis index scores of knee osteoarthritis patients in the electroacupuncture group and shock wave group decreased compared with the control group, and they were statistically significant (P value < 0.05).

Repeated measures of variance were used to analyze the trend of changes in the osteoarthritis index scores of each group before treatment, 2 weeks after treatment, and 4 weeks after treatment. The results showed that the score showed a gradual downward trend over time, and it was statistically significant ($P < 0.05$). There was no statistically significant difference between the electroacupuncture group and the shock wave group. See Table 3 for details.

3.2. Analysis of NRS Scores before and after Treatment. The knee osteoarthritis patients in the control group, electroacupuncture group, and shock wave group were evaluated for NRS before treatment, 2 weeks after treatment, and 4 weeks after treatment. The results showed that there was no statistically significant difference in NRS scores between the three groups before treatment ($P = 0.965$). After 2 weeks and 4 weeks of treatment, the scores of patients with knee osteoarthritis in the electroacupuncture group and shock wave group were lower than those in the control group, and they were statistically significant ($P < 0.001$).

Repeated measures of variance were used to analyze the decline in NRS scores of each group before treatment, 2 weeks after treatment, and 4 weeks after treatment. The change of the decline over time was statistically significant ($P < 0.001$). The decline of NRS scores in the electroacupuncture group and shock wave group was greater than that of the control group. There was no statistically significant difference between the electroacupuncture group and the shock wave group. See Table 4 for details.

3.3. Analysis of WHOQOL-BREF Scale after Treatment. The knee osteoarthritis patients in the control group, the electroacupuncture group, and the shock wave group were scored by WHOQOL-BREF before treatment and 4 weeks after treatment. The results showed that there was no statistically significant difference in the scores of the three groups before treatment. After 4 weeks of treatment, the physical, psychological, and social environment of each group changed significantly. The physiological and psychological scores of patients with knee osteoarthritis in the electroacupuncture group and shock wave group increased compared with those in the conventional group ($P < 0.001$). There was no statistical difference between the three groups after treatment. See Table 5 for details.

3.4. Adverse Reactions. There were no adverse reactions in the electroacupuncture group and shock wave group during the one-month treatment course. The treatment is safe and effective.

Table 2: NRS scoring criteria.

NRS scoring criteria					
	Score				
Pain scale	0	1-3	4-6	7-9	10
	Painless	Mild pain	Moderate pain	Severe pain	Worst pain

Table 3: Score analysis of osteoarthritis index scores before treatment, after 2 weeks of treatment, and 4 weeks of treatment of the three groups (mean(SD)).

Index	Time	Control group ($n = 33$)	Electroacupuncture group ($n = 41$)	Shock wave group ($n = 54$)
Pain	Before treatment	12. (2.89)	12.20 (2.03)	12.23 (2.03)
	After 2 weeks of treatment	8.41 (2.31)	6.34 (2.43)	6.28 (2.52)
	After 4 weeks of treatment	6.29 (1.21)	4.33 (1.92)	4.11 (1.58)
	P	<0.001	<0.001	<0.001
Stiff	Before treatment	4.27 (1.01)	4.52 (1.38)	4.41 (1.26)
	After 2 weeks of treatment	3.41 (1.13)	2.02 (0.93)	2.10 (1.04)
	After 4 weeks of treatment	2.20 (1.29)	1.31 (1.21)	1.23 (1.25)
	P	<0.001	<0.001	<0.001
Daily activity	Before treatment	58.36 (4.81)	59.19 (3.12)	58.77 (3.95)
	After 2 weeks of treatment	43.21 (4.92)	39.18 (3.83)	38.22 (3.83)
	After 4 weeks of treatment	26.23 (3.19)	23.16 (4.28)	22.85 (3.31)
	P	<0.001	<0.001	<0.001
Total score	Before treatment	74.88 (5.27)	75.93 (5.31)	76.07 (5.14)
	After 2 weeks of treatment	55.03 (5.82)	47.57 (4.92)	46.44 (5.37)
	After 4 weeks of treatment	34.72 (3.29)	28.85 (2.96)	27.68 (3.04)
	P	<0.001	<0.001	<0.001

Table 4: NRS score analysis of the three groups before treatment, 2 weeks after treatment, and 4 weeks after treatment (mean(SD)).

Index	Time	Control group ($n = 33$)	Electroacupuncture group ($n = 41$)	Shock wave group ($n = 54$)
NRS score	Before treatment	6.23 (1.27)	6.24 (1.03)	6.25 (1.18)
	After 2 weeks of treatment	5.21 (1.02)	4.07 (1.23)	4.06 (1.19)
	After 4 weeks of treatment	4.07 (1.21)	3.19 (1.24)	3.22 (1.20)
	P	<0.001	<0.001	<0.001

Table 5: NRS score analysis of the three groups before treatment, 2 weeks after treatment, and 4 weeks after treatment (mean(SD)).

Index	Time	Control group ($n = 33$)	Electroacupuncture group ($n = 41$)	Shock wave group ($n = 54$)
Physiology	Before treatment	10.45 (1.12)	10.20 (0.97)	10.33 (1.03)
	After 4 weeks of treatment	12.31 (1.28)	12.89 (1.33)	12.98 (1.40)
	P	<0.001	<0.001	<0.001
Psychology	Before treatment	10.06 (0.68)	10.33 (0.85)	10.39 (0.97)
	After 4 weeks of treatment	12.18 (1.23)	13.07 (1.10)	13.22 (1.26)
	P	<0.001	<0.001	<0.001
Society	Before treatment	13.19 (1.14)	12.89 (1.15)	13.06 (1.16)
	After 4 weeks of treatment	14.33 (1.15)	13.82 (1.31)	14.00 (1.26)
	P	<0.001	<0.001	<0.001
Environment	Before treatment	11.27 (0.94)	11.48 (1.05)	11.37 (1.01)
	After 4 weeks of treatment	12.52 (1.02)	12.64 (0.89)	12.77 (0.99)
	P	<0.001	<0.001	<0.001

4. Discussion

This study found that electroacupuncture combined with drugs and shock wave combined with drugs are more effective than conventional drug treatment in terms of arthritis index. The curative effect increases with the prolonged treatment time. There was no statistical difference between electroacupuncture and shock wave drugs. Clinical studies have shown that this effect may be related to the downregulation of the expression of IL-1β and MMP-3 in the synovial fluid of KOA patients and the upregulation of the expression of SOD [15].

In terms of pain index, electroacupuncture combined with drugs and shock waves combined with drugs are more effective than conventional drug treatments. As the treatment time is extended, the efficacy increases. There was no statistical difference between electroacupuncture and shock wave drugs. Animal experiments have shown that this effect can adjust the metabolic environment of chondrocytes by reducing the content of IL-1β and TNF-α in articular cartilage, inhibit the catabolism of cartilage matrix, and inhibit cartilage degeneration, thereby reducing the damage of articular cartilage.

In addition, in terms of quality of life assessment, electroacupuncture combined with drugs and shock waves combined with drugs are more effective than conventional drug treatment in terms of physiological and psychological indexes. There was no statistical difference between electroacupuncture and shock wave drugs. There was no statistical difference with the conventional group in terms of social environment. There was no statistical difference between the groups before and after treatment. Studies have shown that electroacupuncture can effectively alleviate the symptoms of KOA. The mechanism of action may be related to downregulating the expression of AQP3 to regulate water transport, reduce the degradation of cartilage extracellular matrix, and reduce the destruction of articular cartilage.

The mechanism of this experiment needs to be further studied and proved in the future.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Ethical Approval

The study design and methodology adhered to the principles of the Declaration of Helsinki and were approved by the Shenzhen Longhua District Central Hospital ethics committee (June 2021; approval number).

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Yuhui Zhao contributed mostly. YHZ conceived and participated in the design of the study, established the initial protocol, and drafted the manuscript. Xuebing Wang and Dianquan Zhang participated in the revision of the manuscript. YHZ, DQZ, and XBW participated in the development of the acupuncture protocol. YHZ and XBW participated in the design of and amended the manuscript. All authors read and approved the final manuscript.

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Retraction

Retracted: Design and Application of Electronic Rehabilitation Medical Record (ERMR) Sharing Scheme Based on Blockchain Technology

BioMed Research International

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[1] J. Zhang, Z. Li, R. Tan, and C. Liu, "Design and Application of Electronic Rehabilitation Medical Record (ERMR) Sharing Scheme Based on Blockchain Technology," *BioMed Research International*, vol. 2021, Article ID 3540830, 12 pages, 2021.

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Research Article

Design and Application of Electronic Rehabilitation Medical Record (ERMR) Sharing Scheme Based on Blockchain Technology

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As the value of blockchain has been widely recognized, more and more industries are proposing their blockchain solutions, including the rehabilitation medical industry. Blockchain can play a powerful role in the field of rehabilitation medicine, bringing a new research idea to the management of rehabilitation medical data. The electronic rehabilitation medical record (ERMR) contains rich data dimensions, which can provide comprehensive and accurate information for assessing the health of patients, thereby enhancing the effect of rehabilitation treatment. This paper analyzed the data characteristics of ERMR and the application requirements of blockchain in rehabilitation medicine. Based on the basic principles of blockchain, the technical advantages of blockchain used in ERMR sharing have been studied. In addition, this paper designed a blockchain-based ERMR sharing scheme in detail, using the specific technologies of blockchain such as hybrid P2P network, block-chain data structure, asymmetric encryption algorithm, digital signature, and Raft consensus algorithm to achieve distributed storage, data security, privacy protection, data consistency, data traceability, and data ownership in the process of ERMR sharing. The research results of this paper have important practical significance for realizing the safe and efficient sharing of ERMR, and can provide important technical references for the management of rehabilitation medical data with broad application prospects

1. Introduction

With the rapid development of the rehabilitation medical industry and the rapid increase of rehabilitation medical data, many medical institutions have begun to use electronic rehabilitation medical record (ERMR) to record the status of patients receiving rehabilitation services. Rehabilitation medical record comprehensively records the patient's identity information, medical history, examination results, and the evaluation, diagnosis, and training of rehabilitation medicine. It is an important part of rehabilitation medical work and determines the overall quality of rehabilitation medical treatment. ERMR can provide more convenient storage and query for rehabilitation medical data and store more comprehensive diagnosis information. At the time of diagnosis, the rehabilitation doctor can quickly and accurately understand the patient's medical history through the ERMR, so as to make a more comprehensive and accurate analysis and assessment of the patient's condition.

For comprehensive complex diseases, chronic diseases, and dysfunctions (such as stroke, spinal cord injury, fractures, and osteoarthropathy), patients often need long-term, continuous diagnosis and treatment. A safe, reliable, and easily accessible ERMR will definitely improve the work efficiency of rehabilitation doctors, facilitate the rehabilitation doctors to accurately understand the patient's personalized information and rehabilitation needs, adopt targeted rehabilitation treatment plans, and improve the effectiveness of individual rehabilitation [1]. The sharing of ERMR is also beneficial to rehabilitation research institutions and provides basic data and case references for prospective scientific research [2, 3].

Blockchain is a new distributed infrastructure and computing model which uses the block-chain data structure to verify and store data, uses the distributed nodes and the consensus algorithms to generate and update data, uses the cryptography to ensure the security of data transmission and access, and uses the smart contracts composed of automated script codes to program and manipulate data. As a new computing model that builds trust at a low cost in an untrusted competitive environment, blockchain technology is considered a subversive innovation of computing model. It is changing the application scenarios and operating rules of many industries and is triggering a new technological innovation and industrial transformation on a global scale.

Blockchain is originated from encrypted digital currency and is currently being extended to other fields. As the value of blockchain is widely recognized, more and more industries are proposing their own blockchain solutions, including the medical and health industry. Blockchain can play a very powerful role in the medical field, which is particularly obvious in medical data management [4]. Blockchain is essentially a decentralized distributed storage system, which has great advantages in trust mechanism, data security, privacy protection, etc. Applying it to ERMR sharing will be a good breakthrough point with broad application prospects [5–7].

The application of blockchain technology to the processing of electronic medical data is one of the current hot areas of blockchain research. Electronic medical records can be stored in the blockchain system. However, if all medical data is directly stored in the blockchain network, it will increase the burden of calculation and storage on the blockchain. In order to solve these problems, many related research and applications have adopted a hybrid storage architecture, storing the original medical data in a local database, and only the index of the original data (i.e., the location of the local database) is stored on the blockchain. Zhang and Lin proposed a blockchain-based secure and privacy-preserving personal health information (PHI) sharing scheme for diagnosis improvements in e-Health systems and constructed two kinds of blockchains (namely the private blockchain and the consortium blockchain) by devising their data structures and consensus mechanisms [8]. Shamshad et al. put forward a blockchain-based privacy and security preserving electronic health record (EHR) sharing protocol and constructed two types of blockchains, in which the private blockchain was in charge of storing the EHRs, while the consortium blockchain storing the EHRs' secure indexes [9].

ERMR contains the patient's personal information; so, the confidentiality and security of the data should be ensured when the blockchain technology is applied to electronic medical record sharing. The encryption technology of the blockchain can be used to securely share data between authorized users. Dagher et al. proposed a blockchain-based framework for secure, interoperable and efficient access to medical records by patients, providers, and third parties, while preserving the privacy of patients' sensitive information. The framework utilized smart contracts in an Ethereum-based blockchain for heightened access control and obfuscation of data and employed advanced cryptographic techniques for further security [10]. Haque et al. used the SHA256 secure hash algorithm for generating a unique and identical 256-bit or 32-byte hash value for a particular medical record and focused on five mechanisms (i.e., digital access rules, data aggregation, data immutability, data liquidity, and patient identity) of data transition for securing the medical records at the proposed blockchain model [11].

In the blockchain network, since there is no trusted central authority, reaching a consensus between untrusted nodes is an important issue. Sri and Bhaskari proposed a blockchain-based encryption of patient data among shared network and used the consensus mechanism to validate Proof of Word and interoperability for data discovery and access [12]. Huang et al. proposed a blockchain-based privacy-preserving scheme which realized the secure sharing of medical data and executed a distributed consensus based on PBFT algorithm for transactions between patients and research institutions according to the prearranged terms [13]. Qazi et al. proposed a consensus algorithm titled Proof of Authenticity over the distributed platform for all medical stakeholders, in which hospitals and clinics are assumed the roles of both miners and validators, and designed a smart contract that follows the proof of authenticity mechanism [14].

The Hyperledger Fabric open-source project implements an underlying general framework of the permissioned blockchain, providing scalable applications such as identity verification, P2P protocol, access control, consensus algorithm, and smart contract and can support the application scenarios of blockchain in electronic medical record sharing. CLIM et al. proposed that the access control in the mobile health application can be implemented by using a permissioned blockchain built on the Hyperledger Fabric [15]. Sharma and Balamurugan used a blockchain-based framework Hyperledger Fabric and Composer tool to implement a blockchain-based electronic health record (EHR) network which made the EHRs more secure and private [16]. Usman and Qamar implemented a prototype of Electronic Medical Record Management System using permissioned blockchain platform "Hyperledger" which ensured the security, privacy, and easy accessibility of data [17].

The number of relevant literatures on the application of blockchain technology to the management of electronic medical records has shown a surge, but as far as its research content is concerned, it still has obvious limitations. The vast majority of the existing literatures are technical papers, focusing on the details of blockchain technology, but lack of discussion on the concept, connotation, and management method evolution of electronic medical record in the new technical environment. The existing literature often selects a single technical problem for detailed research, such as the privacy protection of electronic medical record,or the improvement of consensus algorithms, but it lacks the overall and systematic design of blockchain solutions and integrated research framework. The implementation of blockchain solutions in the existing literature mostly stays at the stage of simulation experiments, lacking practical considerations for specific application scenarios. Research on typical industry application cases is rarely involved, and there is a lack of exploratory thinking about the policy and laws that may be faced by the application of the solution. The application of blockchain in the management of electronic medical record is not only a technical issue, but more importantly, it is to study how blockchain creates value in practical applications and how to play its role in reducing costs, improving efficiency, and optimizing the integrity environment.

Based on the application requirements of data sharing in the field of rehabilitation medicine, the data characteristics of ERMR, and the basic principles of blockchain technology, this paper analyzed the technical advantages of blockchain used in ERMR sharing and designed a set of ERMR sharing scheme based on blockchain technology in detail to truly realize the distributed secure storage and sharing of rehabilitation medical data. Comparing the scheme in this paper with some existing blockchain-based medical data sharing schemes, this scheme has greater advantages in data security, system controllability, processing efficiency, etc. This paper deeply integrated blockchain technology and ERMR management, which helped solve the practical problems faced by ERMR management, realized the safe sharing of ERMR, and reduced the cost of ERMR collection, thereby facilitating the technology and efficiency transformation of health care industry and promoting the overall development of the health care service system. In addition, on the basis of theoretical research, this paper made full use of advanced computer technology to design and develop the overall scheme and typical application scenario of the ERMR management based on the blockchain, which will help guide the specific application of blockchain in the health and medical industry, and provide a technical path with industry reference value.

2. Application Requirements of Blockchain in ERMR Sharing

2.1. The Characteristics of Rehabilitation Medical Data. Rehabilitation medicine focuses on the overall rehabilitation of dysfunction, involving the comprehensive and coordinated application of multiple rehabilitation treatments such as physical therapy, occupational therapy, psychotherapy, drug therapy, and plastic therapy. It is usually a long-term treatment. Therefore, the data dimensions of ERMR are more abundant than ordinary clinical medical record, and provide comprehensive and accurate information for the overall assessment of the patient's health status.

Through literature review [18–20], as well as the collection and analysis of the hospitals' rehabilitation medical records, the main data content of the rehabilitation medical records can be summarized as shown in Table 1.

2.2. The Main Problems in ERMR Sharing. ERMR can comprehensively reflect the patient's functional level, health status, living status, etc. It not only involves rehabilitation medical institutions but also involves some important civil affairs departments and social functions [21, 22], such as social welfare, community services, social security for people with disabilities, education, employment, and charities aid. However, from the current situation, ERMR has not yet achieved safe and efficient sharing between different institutions. The main reasons are as follows.

Trust issues. In order to maintain the security of ERMR, doctors and patients will be strictly restricted when accessing data, and a lot of time and resources are needed to conduct permission review and verification. ERMR is a valuable data asset of rehabilitation medical institutions, and external sharing may reduce their own competitive advantages. There is a lack of a reasonable mutual trust mechanism between the owners and users of rehabilitation medical data. The lack of trust has caused serious isolated islands of medical information and hindered the development of medical big data and smart healthcare.

Security of rehabilitation medical data. In the traditional way, ERMR is usually stored in the local database of hospitals. In this centralized storage method, the amount of information in the local database of each hospital is huge [23], which is easy to become a key target of hacker attacks, leading to data leakage and data tampering.

The ownership of rehabilitation medical data. ERMR records the patient's vital data [24]. In theory, the patient should enjoy the priority data ownership. However, the current actual situation is that ERMR is controlled by medical institutions, and patients do not have the actual control capabilities of processing, using, and sharing their own ERMR. Obviously, this mechanism does not reasonably protect the rights and interests of information subjects.

The contradiction between ERMR sharing and patient privacy protection. With the rapid development of the Internet and big data technology, personal information protection has become a focus of attention worldwide. ERMR contains a large amount of sensitive and confidential personal information. Once leaked, it will cause serious data security risks and conflicts between doctors and patients. When ERMR is shared, privacy protection must be strengthened to prevent the leakage of patients' personal information.

The quality of rehabilitation medical data. Since ERMR involves the patient's vital data, the correctness, completeness, and real-time of the data are crucial to the patient's diagnosis and treatment effect. Once the wrong data or false data is entered, it will have a serious negative impact on diagnosis and treatment. Therefore, it is of great significance to implement strict medical data quality management and data traceability. However, because the technical standards of various rehabilitation medical institutions are not uniform, it is difficult to ensure the consistency of rehabilitation medical data, which increases the difficulty of medical information sharing.

With the rise of cloud computing technology, medical institutions can upload ERMR to a third-party cloud server, and the ERMR can be hosted by a third-party cloud service agency [25]. This method improves the efficiency of storage, retrieval, and sharing of ERMR to a certain extent. However, cloud servers are generally considered semitrusted. When all

Table 1: Main data content of rehabilitation medical record.

Data category	Main content
Patient identification	Name, ID number, gender, date of birth, home address, etc.
General health	Nutritional status, excretion method, bowel function, sleep mode, safety issues, mental status, language, hearing, vision, activity status, self-care status, etc.
Past medical history	History of disease, infectious disease, allergy, vaccination, surgery, trauma, blood transfusion, etc.
History of present illness	The cause, main symptoms, duration, degree of impact of the dysfunction, the status of receiving rehabilitation treatment, etc.
Professional and psychosocial history	Occupation, lifestyle, economic status, history of marriage and childbirth, family status, living environment, mental state, interests and hobbies, etc.
Physical examination	Body temperature, pulse, blood pressure, respiration, weight, urinalysis, skin damage, etc.
Specialist examination	Nervous system and musculoskeletal system examination and measurement, such as advanced brain function, neural reflex, gait analysis, joint range of motion, muscle tone, hand muscle strength, balance disorder, and upper and lower limb function
Functional rating scale	Activity of Daily Living Scale (ADL), NIH Stroke Scale (NIHSS), European Stroke Scale (ESS), Brunnstorm Motor Function Rating, Fugl-Meyer Assessment (FMA), wolf motor function test (WMFT), manual muscle testing (MMT), range of motion (ROM), Modified Rankin Scale (MRS), Modified Ashworth Scale (MAS), Berg Balance Test, Function Independent Measure (FIM), Modified Barthel Index (MBI), etc.
Laboratory and instrument examination	Center of gravity measurement, stability limit evaluation, smart Equitest balance master, imaging examination, etc.
Diagnosis	Disease diagnosis, dysfunction diagnosis, complications, etc.
Treatment plan	Preliminary rehabilitation goal, rehabilitation method (such as physical therapy, occupational therapy, speech therapy, etc.), types of medications, prevention of systemic risks in rehabilitation medicine, etc.
Rehabilitation assessment	Short-term and long-term goals of rehabilitation treatment, current treatment plan, treatment points, and precautions

the rehabilitation medical data are stored in a centralized cloud server, once the cloud server is not well supervised or suffers a targeted malicious attack, it will cause all the rehabilitation medical data to be leaked, tampered, or even lost. The consequences will be very serious.

2.3. The Advantages of Applying Blockchain to ERMR Sharing. The P2P (peer-to-peer) network structure of blockchain can realize the distributed storage of ERMR. Distributed storage of massive ERMRs on multiple servers can effectively use the large and scattered storage and computing resources in the network, achieving the mass storage and high-performance computing of rehabilitation medical data [26]. There is no centralized node in the P2P network. Even if one of the nodes fails, it will not affect the normal operation of the entire blockchain system;so, the stability of the system is superior. Nodes can directly transmit data without going through a third-party centralized node, which can effectively reduce the risk of information leakage.

The blockchain data structure of the blockchain can ensure that the ERMR cannot be tampered with and can be traced. Under the blockchain data structure, blocks are created in chronological order and are connected into a chain by hash value, which can be traced back to the first block. The blockchain data structure can ensure that the ERMR cannot be tampered with, so that the original rehabilitation medical data maintains a high degree of consistency and integrity [27]. The timestamp in the block records the generation time of each block and the entry time of each medical data, making it easier to trace medical data and further increasing the difficulty of tampering with data, providing more credible and comprehensive protection for the ERMR.

The hash function of the blockchain can realize the privacy protection of patients. The hash encryption function can map the rehabilitation medical data into a string of garbled hash values composed of numbers and letters, and there is no way to reverse and decrypt it. The hash function can be used to encrypt personal identification data and sensitive data in the ERMR and strengthen the privacy protection of patients.

The asymmetric encryption algorithm and digital signature of the blockchain can strengthen the security of rehabilitation medical data. The asymmetric encryption algorithm uses public and private keys to encrypt and decrypt data, respectively, greatly reducing the risk of information leakage during information transmission, thereby ensuring the security of ERMR. Digital signature technology can realize user identity verification and prevent unauthorized users from accessing the ERMR.

The consensus mechanism of the blockchain can achieve "trust-free" and better promote the participation of medical institutions in ERMR sharing. The consensus mechanism solves the trust problem through mathematical algorithms and forms a new type of trust mechanism without the mutual trust between medical institutions [28]. At the same time, medical data ownership issues can be determined through the consensus mechanism, making medical data truly an asset with clear property rights and clear value.

3. Basic Principles of Blockchain Technology

Blockchain is not a single information technology, but an innovative combination of existing information technologies such as distributed data storage, point-to-point transmission, consensus mechanism, and encryption algorithm, so as to realize a new application mode in the Internet era. It has the technical characteristics of distributed storage, partial decentralization, quasianonymity, security, credibility, open source, and programmability, which can solve the difficult problems in the ERMR sharing in a targeted manner.

3.1. Peer-to-Peer (P2P) Network. The blockchain uses a peer-to-peer (P2P) network structure (see Figure 1) to organize all network nodes. It does not have a centralized node, but uses distributed storage technology, and each node stores a copy of the complete data. It can be seen that the blockchain is essentially a decentralized distributed database, and the block data is stored by all nodes in the blockchain system.

3.2. The Blockchain Data Structure. In the blockchain, data is organized and stored in a blockchain data structure. Each block can be divided into two parts, the block header and the block body. The blocks are created in chronological order and connected into a chain by block hash (also called block ID), as shown in Figure 2. The block header records the control information such as block version, block height, block hash, previous block hash, Merkle tree root, block timestamp, difficulty, and block nonce. The block body contains all the specific transaction data in this block and is stored in a Merkle tree structure. The leaf nodes are paired in pairs, and the hash operation is performed upwards until the root of the Merkle tree in the block header.

3.3. The Hash Encryption Function. The hash algorithm is one of the core technologies of blockchain. It is a collective name for a series of hash encryption functions. Through the hash function, the transaction information of any length in the block can be mapped into a series of fixed length hash values (similar to garbled codes) composed of numbers and letters, thereby hiding specific information. For example, the SHA-256 algorithm can convert the transaction data of any length into a string of 64 numbers or letters. The hash function is one-way and cannot be reversed and decrypted. It can be used to encrypt identity data and sensitive data to strengthen the privacy protection of the information subject.

The transaction data in the block body is hashed upward in a pairwise manner in the Merkle tree. This storage method can ensure that the transaction data cannot be tampered with. Once a piece of transaction data is modified, the Merkle tree of the block needs to be hashed again, so that the Merkle tree root and the block hash in the block header are changed and no longer match the next block.

3.4. The Asymmetric Encryption Algorithm. Each node in the blockchain has a unique pair of public and private keys. The public key is open to the outside world, indicating the identity of the node, and the private key is not open, indicating the right to control the information. Information encrypted with one of the keys can only be decrypted by the corresponding other key. The basic principle of asymmetric encryption algorithm is shown in Figure 3. When sending information, the sender A uses the public key of the receiver B to encrypt the information, and the information is transmitted on the network in the form of ciphertext. After receiving the information, the receiver B uses its private key to decrypt the information.

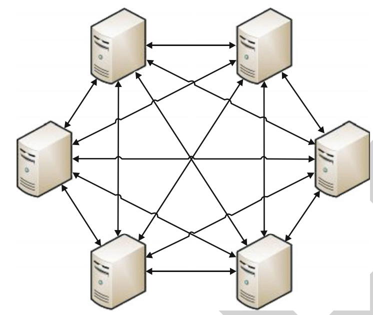

Figure 1: The P2P network structure.

3.5. The Consensus Mechanism. The consensus mechanism is a mechanism that uses mathematical algorithms to create trust between nodes without central control. The data in the blockchain system is stored independently by all nodes. Under the coordination of the consensus mechanism, the data consistency of each node can be guaranteed. The consensus algorithm of the public blockchain is represented by Proof of Work (PoW), Proof of Stake (PoS), and Delegated Proof of Stake (DPoS), and the data writing order adopts the "write first and then consensus" method. The consensus algorithms of the private blockchain and the consortium blockchain mainly include Practical Byzantine Fault Tolerance (PBFT) and Raft, using the "consensus first and then write" data writing sequence.

3.6. The Smart Contract. Smart contract is the computer program deployed on the blockchain. It implements, compiles, and deploys the business logic of the blockchain system in the form of program code. Once the established conditions are met, it can be triggered and automatically executed, minimizing the manual intervention. The smart contracts of mainstream blockchain platforms are shown in Table 2.

4. Materials and Methods

4.1. The Network Structure Design. In order to realize the safe sharing of rehabilitation medical data under the premise of ensuring system controllability, in terms of network structure, a "partially decentralized" hybrid P2P network model can be adopted, as shown in Figure 4. Rehabilitation hospitals, rehabilitation centers, rehabilitation research institutes, insurance companies, regulatory authorities, and other institutions act as super nodes in a distributed network to form a consortium blockchain. Each super node and several ordinary nodes (i.e., patients) form a partial centralized network centered on the medical institution. Hybrid P2P network has

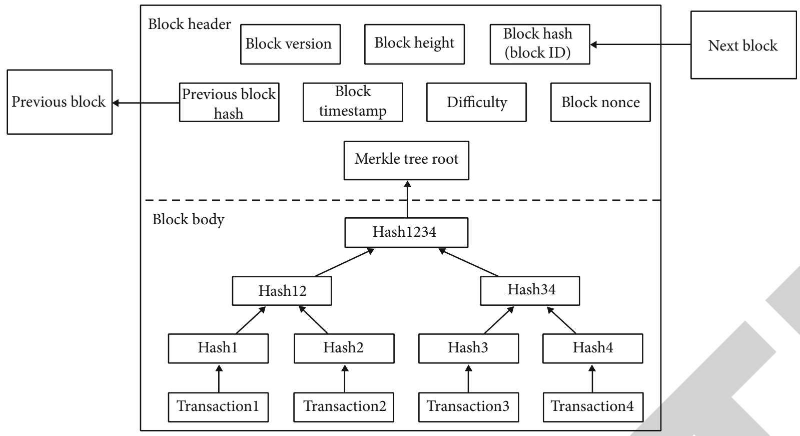

Figure 2: The blockchain data structure.

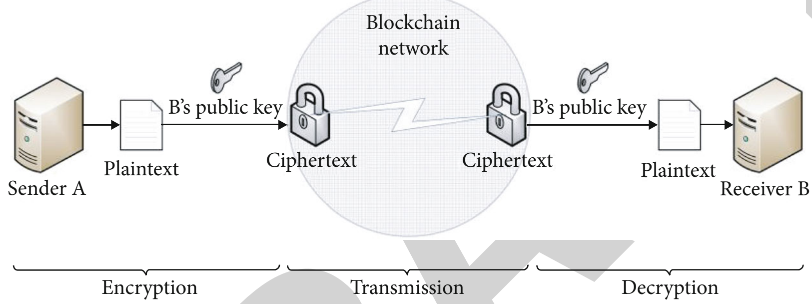

Figure 3: The basic principle of asymmetric encryption algorithm.

Table 2: The smart contracts of mainstream blockchain platforms.

Blockchain platform	Development language	Operating environment
Bitcoin	Script	/
Ethereum (ETH)	Solidity/serpent	EVM
Hyperledger Fabric	Go/Java	Docker
R3 Corda	Kotlin/Java	JVM

a flexible structure and is less difficult to implement, which is more common in practical applications.

4.2. The Data Storage Design. In a hybrid P2P network, in order to ensure the security of the data on the blockchain and overcome the storage space limitations and performance bottlenecks of the blockchain, an on-chain-off-chain hybrid storage mechanism can be used. The ERMR can be divided into two parts: the detailed information and the summary information. The detailed ERMR is stored in the local database of each medical institution in an encrypted manner, and the summary information of the ERMR is stored on the consortium blockchain.

The detailed information of the ERMR includes the rehabilitation doctor ID, patient ID, ciphertext of the ERMR, keyword index, and digital signature of the rehabilitation doctor (see Figure 5). The ciphertext of the medical record is encrypted using the patient's public key, and its content mainly includes the encrypted description of the condition, examination records, treatment records, and consultation time. The keyword index extracts meaningful words from the original record of the ERMR as an index, pointing to the storage location of the ERMR file. The digital signature of the rehabilitation doctor is used to verify the identity of the doctor to ensure the authenticity of the rehabilitation medical data.

The summary information of ERMR is stored on the consortium blockchain using a blockchain data structure. The hospital server creates a new block at regular intervals, in which the summary information of ERMR is stored, and all the blocks are connected into a chain in the order of creation time. Each block consists of two parts: the block header and the block body (see Figure 6).

In the block header, the block hash is the hash value used to uniquely identify the block. The blocks are linked by the hash value of the previous block (that is, the parent hash). The block timestamp records the generation time of each block. In the block body, the ERMR summary information is stored in a Merkle tree structure, which can be used to verify the authenticity and integrity of medical data. The main content of the ERMR summary information includes hospital server ID, patient ID, keyword index, digital signature of the hospital server, and transaction timestamp. The digital signature of the hospital server is used for identity verification to ensure that the data on the blockchain is authentic and reliable. Transaction timestamp records the entry time of each summary information, accurate to the millisecond.

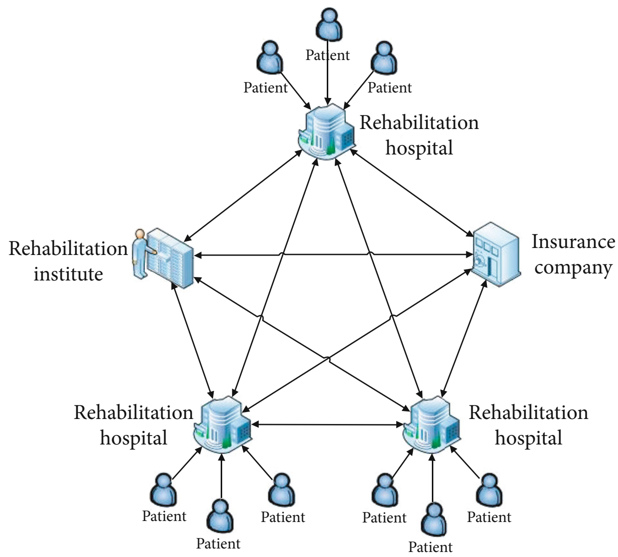

Figure 4: The hybrid P2P network structure.

Details of ERMR
- Rehabilitaiont doctor ID - Patient ID - ERMR encrypted with patient's public key - Keyword index - Digital signature of doctor

Figure 5: The storage structure of the detailed information of ERMR.

It adds a time dimension to the rehabilitation medical data, making it easier to trace and supervise.

The ERMR do not need to be shared globally, only the super nodes on the consortium blockchain can obtain the summary information of ERMR. When medical institutions need to query external data, the consortium blockchain forwards the query request to the provider of the original ERMR based on the ERMR summary information. This method realizes the separation of block data and business data, so that medical institutions can not only realize the point-to-point query of ERMR, but also reduce the risk of medical data leakage. In addition, it can effectively reduce the pressure of high-frequency access to the consortium blockchain and ensure the read and write performance of the block data.

4.3. The Data Transmission Mode Design. Before logging in to the blockchain system, doctors, patients, and third-party institutions need to register, create unique digital identities, and generate their own key pair, in which the public key is externally exposed, and the private key is not. The data transmission process is as follows (see Figure 7).

(1) The patient goes to the hospital for treatment, and the patient's public key information is contained in the medical card

(2) The rehabilitation doctor enters the ERMR for the patient, encrypts the ERMR with the patient's public key, and generates a keyword index. The detailed information of the ERMR such as the patient ID, ERMR ciphertext, and keyword index is stored in the hospital's local database

Summary of ERMR
Block header - Block hash - Previous block hash - Block timestamp - Merkle tree root Block body - Transaction list - Hospital server ID - Patient ID - Keyword index - Digital signature of hospital server - Transaction timestamp

Figure 6: The storage structure of the ERMR summary information.

(3) The hospital server creates a new block at regular intervals to upload the ERMR summary information such as the hospital server ID, patient ID, and keyword index to the consortium blockchain. Other nodes on the consortium blockchain are responsible for verifying the transaction, and if the verification is passed, the new block is created

(4) When the patient goes to other hospitals, if the rehabilitation doctor needs to know the patient's medical history, he can search through the ERMR summary information on the consortium blockchain and send the query request to the provider of the original ERMR. The data provider encrypts the detailed information of the ERMR with the patient's public key and sends it to the inquirer. After receiving the information, the inquiring party uses the patient's private key to decrypt the ERMR and read the content of the medical record with the patient's authorization. Without the authorization of the patient, the detailed information of the ERMR cannot be decrypted, thereby reducing the risk of the leakage of the patient's personal information and protecting the privacy and legal rights of the information subject

(5) If a third-party institution (such as the insurance company, the rehabilitation research institution, etc.) needs to access the patient's ERMR, it needs to obtain the patient's authorization and decrypts the ERMR with the patient's private key. Smart contract can be used to achieve an automated incentive mechanism, and the more the patient's ERMR is queried, the greater the value of the data. The patients can get rewards from ERMR sharing, thereby ensuring the economic interests of the information subject and returning the data ownership to the patient

4.4. The Digital Signature Design. First, the private key k and the public key K of the sender's hospital server need to be generated. The description of the relevant variables is as follows.

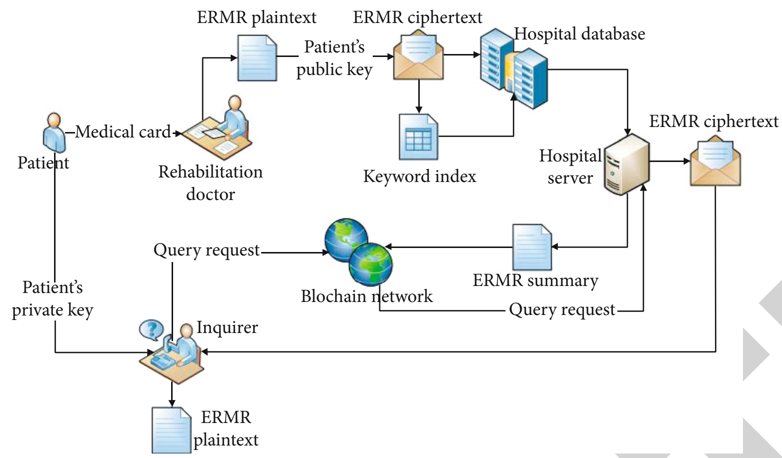

Figure 7: The transmission process of the rehabilitation data.

M-plaintext of the ERMR.
h-hash value of the ERMR.
$G(x, y)$-base point on the elliptic curve.
k-private key of the sender.
K-public key of the sender.
r-random number.

Take a base point $G(x, y)$ on the elliptic curve and set $K = kG(x, y)$. The specific process for the hospital server to generate a digital signature is as follows (see Figure 8).

(1) Use a hash function to map information M to a hash value h

(2) Choose a random number r and calculate the point $rG(x, y)$

(3) Use the private key k of the hospital server to encrypt the hash value h, calculate $s = h + kx/r$, and get the digital signature $\{rG(x, y), s\}$

(4) Upload the information M and the digital signature $\{rG(x, y), s\}$ to the consortium blockchain together

The specific process for the inquirer of the ERMR to verify the digital signature is as follows (see Figure 9).

(1) Find the hash value h according to the information M

(2) The receiver uses the public key K to decrypt the digital signature and calculate $(hG(x, y)/s) + (xK/s)$

(3) Compare whether it is equal to $rG(x, y)$, so as to verify whether the information comes from the sender

The derivation process of the verification principle is as follows.

$$\frac{\mathrm{hG(x,y)}}{\mathrm{x}} + \frac{\mathrm{xK}}{\mathrm{s}} = \frac{\mathrm{h}}{\mathrm{s}}\mathrm{G(x,y)} + \frac{\mathrm{x}}{\mathrm{s}}\mathrm{kG(x,y)} = \frac{\mathrm{h+kx}}{\mathrm{s}}\mathrm{G(x,y)} = \frac{\mathrm{r(h+kx)}}{\mathrm{h+kx}}\mathrm{G(x,y)} = \mathrm{rG(x,y)}. \quad (1)$$

4.5. The Consensus Algorithm Design. ERMR sharing based on the consortium blockchain is an application scenario in a trusted environment, and the security is higher than the public blockchain scenario; so, the consensus algorithm is more suitable for the non-Byzantine Raft algorithm, which can achieve data consistency under the premise that more than half of the nodes in the system are operating normally. The Raft algorithm divides time into a series of terms. During each term, all nodes vote to elect a leader. The leader is given the right to keep accounts during the term and is responsible for generating the new blocks. Until the next term, the system elects a new leader.

Each node in the consortium blockchain has three states: leader, follower, and candidate. Under the normal circumstances, there is only one leader in one term, and all other nodes are followers. When the follower does not receive a response from the leader for a certain period of time (usually 150-300 milliseconds), the system converts to the candidate state, and a new leader needs to be elected.

Assuming there are N nodes in the consortium blockchain, $R_1, R_2, \ldots, R_N$ represent the nodes in the consortium blockchain, $S_1, S_2, \ldots, S_N$ represent the state of each node (i.e., leader, follower, or candidate), and v represents the number of affirmative votes. The leader election steps are as follows (see Algorithm 1).

(1) In the candidate state, the node R_1 sends a REQUEST to the other N -1 nodes, requesting to elect itself as the leader

(2) If other nodes agree, then vote for it

(3) When the affirmative votes reach $(N/2) + 1$, it means that the affirmative votes account for the majority, the node R_1 becomes the leader, and the other nodes become the followers

After the leader R_1 is selected, the process of log replication is as follows (see Algorithm 2), in which u represents the number of nodes who agree to append the record, and $c_1, c_2, \ldots, c_N$ represent the state of the new record (i.e., committed or uncommitted) in the node R_i.

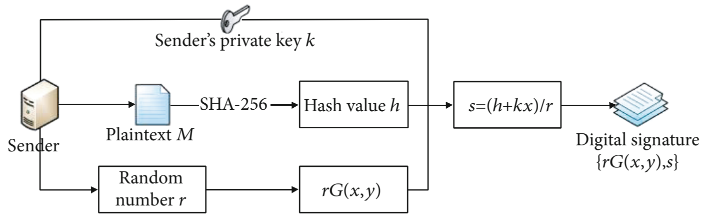

FIGURE 8: The generation process of digital signature.

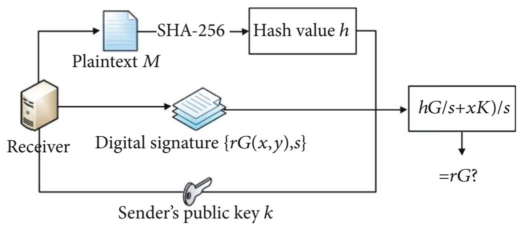

FIGURE 9: The decryption process of digital signature.

(1) The client sends a REQUEST to append a new transaction record to the leader R_1

(2) The leader R_1 appends the new record to its log

(3) The leader R_1 issues an INSTRUCTION to all the followers, asking them to append the new record to their respective logs

(4) When most of the followers agree to append the record to their logs, the addition of the record is confirmed, and then the leader R_1 will send the client a MESSAGE of successful record entry

(5) The leader R_1 informs all the followers to add the confirmed record to their logs

During this process, if a network communication failure occurs and the leader R_1 cannot access most of the followers, the blockchain system will switch to the candidate state and the leader will be reelected. During the loss of connection, any update of the original leader R_1 cannot be confirmed, and all transactions will be rolled back.

Input: The REQUEST to elect R_1 as leader.
Output: S_i.

```
if S_1 == candidate then
    for i = 2 to N do
        R_1 send R_i a REQUEST to elect R_1 as leader
    end for
    v = 0
    for i = 1 to N do
        if R_i agree to elect R_1 as leader then
            R_i vote yes
            v + = 1
        end if
        if v > (N/2) + 1 then
            R_1 is elected as leader
            S_1 = leader
            for i = 2 to N do
                S_i = follower
            end for
            break
        end if
    end for
end if
```

ALGORITHM 1: Algorithm on leader election

5. Results and Discussion

5.1. Results. The ERMR sharing scheme proposed in this paper can be developed and deployed on the basis of the Hyperledger Fabric framework, and smart contracts are written in Go language. In the smart contract, the Go program code to import the Fabric framework is as follows:

```
import ("github.com/hyperledger/fabric/core/chaincode/shim"sc"github.com/hyperledger/fabric/protos/peer")
```

Define a struct in the smart contract to store the ERMR summary information, and the code is as follows:

```
type Summary struct {ServerId string PatientId string Keyword string
}
```

In order to verify the feasibility of the scheme, 110 rehabilitation electronic medical records were collected as test cases. In the Fabric1.4 environment, five orderer nodes (i.e., orderer 1, orderer 2, orderer 3, ordererer 4, and orderer 5) were built to provide the consensus service. The configuration of the test environment is shown in Table 3.

First, stop the server of Orderer5, and the system can respond to the client request normally. Then, stop the server of Orderer4, and the system can still respond to the client request normally. Then, stop the server of Orderer3, and at this time, the client's request cannot be responded to. As can be seen, under the action of the Raft consensus algorithm, data consistency can be achieved, and the blockchain network with 5 nodes can tolerate the failure of up to 2 nodes.

5.2. Discussion. The scheme proposed in this paper helps to realize the safer and faster sharing of ERMR, the rehabilitation hospitals, rehabilitation centers, communities, insurance companies, research institutions, government departments, and other institutions can benefit from it, so as to better facilitate the development of smart healthcare.

Input: REQUEST from the client.
Output:c_i
client send R_1 a REQUSET to add a record
R_1 append the record to its log
$c_1 = uncommitted$
for $i = 2$ to N **do**
  R_1 send R_i an INSTRUCTION to append the record
end for
$u = 0$
for $i = 1$ to N **do**
  if R_i agree to add the record **then**
    $u + = 1$
  end if
  if $u > (N/2) + 1$ **then**
    the addition of the record is confirmed
    $c_1 = committed$
    R_1 send the client a MESSAGE of successful record entry
    break
  end if
end for
for $i = 2$ to N **do**
  R_1 inform R_i to append the confirmed record
  R_i append the record to the log
  $c_i = committed$
end for

Algorithm 2: Algorithm on log replication

Table 3: Configuration of the test environment.

Item	Version/parameter
Operating system	Ubuntu 16.04 TLS
CPU	Intel i7 7700
Memory	16G DDR4
Hard disk	1 T HDD
Hyperledger Fabric	1.4.1

The scheme proposed in this paper has the following potential application scenarios.

Diagnosis and treatment of chronic diseases. Patients with chronic diseases need long-term and continuous treatments, and various related parties are involved during the treatment, such as rehabilitation doctors, rehabilitation therapists, and third-party service agencies. The ERMR sharing scheme based on blockchain technology can break the access barriers between different medical institutions, so that the doctors can track the patient's historical diagnosis and treatment and reduce the waste of resources caused by repeated diagnosis and treatment. It can establish trust between various stakeholders, so that all relevant parties can share information in a protected environment and realize the full-process sharing and collaboration of chronic disease treatment.

Supervision and control of rehabilitation medical services. The rehabilitation medical record is an important basis for handling medical disputes. However, under the current technical conditions, rehabilitation medical record may be tampered with when a medical accident occurs, which makes it difficult to provide evidence and determine responsibility, and cause escalation of doctor-patient conflicts. The nontamperable feature of blockchain can solve this problem. In the event of a medical accident, the specific responsible person can be identified, achieving the effective control of the quality of rehabilitation medical services.

Medical insurance claims. The current process of medical insurance claims usually involves the applicant paying the treatment fee to the hospital first and then claiming compensation from the insurance company after obtaining the payment list from the hospital. The whole process is complicated and time-consuming. By using the blockchain technology, the insurance company can obtain the medical expense data in real time. Smart contract can realize the automatic verification of insurance contracts and automatic execution of claims, thereby improving the efficiency of claims processing. The nontamperable feature of blockchain can effectively reduce the medical fraud caused by tampering with medical records.

Clinical research in rehabilitation medicine. ERMR sharing can provide important basic data and case reports for clinical research of rehabilitation medicine. On this basis, rehabilitation researchers can perform medical record analysis and data mining to better serve the rehabilitation clinical treatment.

Supervision and traceability of rehabilitation medicine. Regulatory authorities can obtain credible rehabilitation medical data in real time, grasp the overall status of residents' chronic diseases, and evaluate the overall living conditions of disabled people in society, thus greatly improving the efficiency of supervision and providing a basis for formulating relevant policies.

6. Conclusions

Specifically, the contributions of this paper mainly included the following aspects.

This paper adopted a hybrid P2P network structure, used hospitals, research institutes, insurance companies, civil affairs departments, and other institutions as super nodes, designed a hybrid P2P structure alliance chain. While realizing the distributed storage of ERMR, the controllability of the system was better maintained.

An on-chain-off-chain hybrid storage mechanism was designed in this paper. The detailed information of the ERMR was stored in the local database of each hospital, and the summary information of the ERMR was stored on the consortium blockchain in a block-chain data structure. This storage mechanism could not only realize the point-to-point query of ERMR between different hospitals but also effectively solve the attack problem under the centralized storage on third-party cloud servers, thereby effectively reducing the risk of medical data leakage and ensuring the read and write performance of data on the blockchain under the condition of increasing data volume.

The asymmetric encryption algorithm was used in this paper to realize the safe sharing of ERMR. The public key and private key were used to encrypt and decrypt the ERMR. The private key was not transmitted on the blockchain network, which greatly reduced the risk of information leakage. Only after being authorized by the patient and obtaining the patient's private ke, could the medical institution be able to read the content of the ERMR, thereby strengthening the protection of the patient's personal information and avoiding the legal and ethical risks caused by medical data sharing in the traditional way.

The digital signature technology was used to realize the identity verification of the hospital server and strengthen data security. Based on the hash algorithm and asymmetric encryption algorithm, the digital signature has been designed. When the hospital server sent the information, it encrypted the hash value of the information with its own private key as a signature and sent the information and the signature to the receiver. The receiver used the message, signature, and the sender's public key to perform calculation and comparison. If they were consistent, the verification passed.

Based on the Raft algorithm, the consensus mechanism of the consortium blockchain was designed, which could solve the system crash caused by node server failure or network communication failure, thereby effectively improving the fault tolerance of the system and ensuring the consistency of data in the blockchain network.

Data Availability

The electronic rehabilitation medical record data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Acknowledgments

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Retraction

Retracted: Research Progress of Deep Learning in the Diagnosis and Prevention of Stroke

BioMed Research International

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This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope

(2) Discrepancies in the description of the research reported

(3) Discrepancies between the availability of data and the research described

(4) Inappropriate citations

(5) Incoherent, meaningless and/or irrelevant content included in the article

(6) Manipulated or compromised peer review

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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Review Article

Research Progress of Deep Learning in the Diagnosis and Prevention of Stroke

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In order to evaluate the importance of deep learning techniques in stroke diseases, this paper systematically reviews the relevant literature. Deep learning techniques have a significant impact on the diagnosis, treatment, and prediction of stroke. In addition, this study also discusses the current bottlenecks and the future development prospects of deep learning technology.

1. Stroke

Stroke (cerebral stroke), also known as "stroke," "cerebrovascular accident" (cerebralvascular accident, CVA), is an acute cerebrovascular disease, characterized by high morbidity, high mortality, and high disability rate, accounting for 40% of the world's stroke deaths, the disability rate is as high as 70%, of which more than 40% of the severe disability [1], and the leading cause of death and disability accounting for about 12% of all deaths [2] poses a threat to human life health and work. In the acute stage of stroke, it is very important for clinicians to make accurate and rapid decisions, such as whether to use thrombolytic drugs or surgical intervention to preserve the damaged site. Medical imaging is the key method to diagnose ischemic stroke and the important basis for clinicians to choose treatment, where CT shows low density and DWI shows high signal that can identify ischemic tissue. Using these images, researchers can detect ischemic lesions and predict possible future lesions. At present, personal manual lesion tracking is still the gold standard for stroke lesion segmentation [3]. However, manual tracking takes a lot of time and labor, and even skilled operators take hours to mark. Therefore, how to objectively and accurately evaluate the information of ischemic stroke patients is a major challenge in clinical practice, which is particularly important for early warning of the high-risk population of ischemic stroke and reducing the incidence of stroke [4, 5]. The application of modern algorithms and data acquisition is particularly important. Diagnosis of early screening for ischemic stroke with deep learning [6] , automatic identification of the infarct size [7], and identification of vascular occlusion [8] all have better effect.

2. Deep Learning

Computer came out in the 1940s. With the development of more than 70 years, computer, as a new subject, not only involves natural science, computing, and other fields. In these only decades, computers have brought us progress in production and life. At the same time, human civilization has moved to a new level in the historical process. As the main function of the machine, the classical computing method includes decision tree, naive Bayes classification algorithm, random forest, *k*-means algorithm [9]. However, when we solve more and deeper practical problems, we find that traditional algorithms have many drawbacks. Artificial intelligence (artificial intelligence) was first proposed at the Dartmouth Conference in 1956 and belongs to the field of computer science [10]. The core of artificial intelligence is machine learning [11]. A mathematical method for simulating human neural network—deep learning—has been developed with the continuous upgrading and development of computer equipment. Malathi et al. [12] proposed mixed reasoning to predict disease and builds up K-nearest neighbor sum, fuzzy set theory, and case reasoning. The results show that this model can improve prediction accuracy. Shamdman et al. [13] developed a heart disease prediction system based on machine learning, a heart disease prediction system was developed. Through crossvalidation, the prediction accuracy of the SVM model was the highest. A team at Kyoto University in Japan used a deep neural network to read and translate human ideas, and "deep picture reconstruction" went beyond binary pixel information [14].

Recently, deep learning (DL, deep learning) has made outstanding contributions to industry and has been widely used in many other disciplines, especially in medical clinic to solve practical problems. It is a hot spot in the medical field. It uses multilayer artificial neural network (artificial neural network, ANN) to simulate the human brain [15]. The ANN is inspired by the CNS neural network, which consists of nodes connected together to form a network with variable weights between different connections. Just as countless neurons form our cerebral cortex, when humans perform daily functional activities, neurons release electrical signals to the central nervous system and other neurons, which people collect and apply various algorithms. Such as depth learning algorithm, these electrical signals are analyzed to guide the model construction. This is of great practical significance to realize artificial intelligence and deep analysis of brain working principle, leading machinery to "intelligence."

3. Application of Depth Learning in Stroke Diagnosis

The division of the infarct size in early ischemic stroke is of great significance for the diagnosis and prediction of disease development. Stroke patients can determine the type of disease by CT, its price parity, noise impact that is small, and imaging speed that is better than other magnetic resonance imaging techniques [16, 17]. Then, there is the disadvantage of being unable to distinguish abnormal lesions. Magnetic resonance imaging can avoid this disadvantage, but it is expensive and inefficient [18]. Chen et al. [19] found that the DWI has the advantage of early diagnosis of acute ischemic stroke and can distinguish the boundary of new and old infarct, but due to time and technical constraints, it is difficult that MRI manually divide the early infarct volume. The Dice score of small lesions is 0.61 and that of large lesions is 0.83. The application of deep learning can mainly make diagnosis accurate and fully automatic. Yang [3] summarized the current segmentation methods and the development of deep neural network research and studies the depth learning-based segmentation methods for chronic or subacute stroke. A crosslayer fusion and contextual reasoning network (CLCI-Net) for T1-weighted images are proposed. Visual system and auxiliary analysis system are designed to reduce the pressure of clinician diagnosis and the error of subjective judgment. Acute ischemic stroke is difficult to detect in CT, and MRI perfusion images can detect key ischemic lesions; so, Chen [20] conducted the research of MRI data around stroke—MRI high precision segmentation of two-dimensional and three-dimensional fully convolutional neural networks—is based on level set [21], FCM based [22], and multiscale CNN [23].D sensitivity and accuracy of the D depth residual network are the highest compared with that of 3D cascaded non-symmetric residual U-Net. As an important part of stroke diagnosis, rehabilitation medicine has gradually moved towards intelligence, precision, and individuation, among which precision evaluation is the main direction. Lang [24] presents a series of automatic evaluation methods of the stroke upper limb motor function based on the depth learning system and puts forward a cyclic neural network model based on time attention for upper arm motion. Brunnstrom is the accuracy of expression by stages that can reach 100. The determination coefficient of the hand motor function score and clinician score can reach 0. A visual depth sensor was introduced to evaluate the function of the upper limb movement, which can track the position of upper limb bone space in real time. The agreement between automatic Fugl-Meyer score and clinician score was as high as 0.89. Image segmentation accuracy CT intracerebral hemorrhage is the basis of preventing early hematoma expansion in patients. However, there are many problems, such as blurred image edge, cavity phenomenon, and uneven gray scale. Wei [25], combining with the present, an algorithm model for image segmentation of cerebral hemorrhage CT based on curve evolution can automatically locate the hematoma suspected area profile, combining symbolic pressure functions with Letan polynomials, to improve the traditional calculation method. The above problems have been solved. Acute ischemic stroke (Als with large vessel occlusion,) with macrovascular occlusion Als-LVO) is one of the leading causes of stroke. Although intravenous thrombolysis is intravenous thrombosis, IVT is an effective way to treat Als, but the revascularization rate for the LVO of treatment is low. The curative effect is not good. Deep learning has been gradually applied to standardized LVO stroke diagnosis in recent years. Research shows that the sensitivity of CNN detection LVO is higher than that of the random forest algorithm (85% : 68%). Deep learning can improve the diagnosis rate of LVO stroke, increasing the speed of clinical work [26]. White matter hyperintense (white matter hyperintensity, WMH) is an imaging feature of diffuse small cerebral vascular disease and brain atrophy. WMH accurate segmentation of stroke lesions is related to the deep study of clinical medicine and epidemiology. WMH previous manual segmentation is very complicated, Guerrero, etc. [27] found that the convolution neural network can accurately distinguish the two lesions, and the CNN architecture is superior to other algorithms. The team of Mark and Mary Stevens Institute of Neuroimaging and Informatics (INI) at the University of Southern California, Stroke, said that they found an alternative, and this method allows clinicians to assess stroke damage without palliative injection of contrast media. Both magnetic resonance imaging and computed tomography require chemical contrast agents, and some contain high doses of X-radiation. Others may be harmful to patients with kidney or vascular disease. The depth learning algorithm designed by Wang Jiong's team can be derived from a safer type of the brain scan (pseudocontinuous artery spin-labeled magnetic resonance imaging, automatic extraction of stroke damage data in pCASL MRI). In the evaluation of brain damage in stroke patients, the pCASL deep learning model achieves 92% accuracy on both independent datasets and reduced damage during diagnosis [28].

4. Application of Depth Learning in Stroke Treatment

Collateral circulation can maintain the ability of brain tissue regeneration and is a determinant of the degree of recovery of ischemic stroke. Computer tomography (CTA) is widely used in the diagnosis of vascular diseases, which can provide important information of collateral circulation and is an important marker for evaluating collateral status. The application of deep learning function to the computer system can improve the ICC of consistency of CTA lateral branch cycle score from 0.58 to 0.77. Automatic CTA can provide objective collateral cycle score, which is highly consistent with expert CTA-CS and improves the reliability of CTA-CS. In conclusion [29], Ho et al. [30] use the method of deep learning, 118 cases of onset time were extracted to determine the specific onset time of patients. The combination of arterial spin labeling (ASL) and deep learning provides a more scientific treatment for acute ischemic stroke (AIS), which can better identify the low perfusion area. The area under the ROC is 0.958, which is better than the traditional algorithm [28]. TOAST classification is currently the most widely used stroke classification system, Ravi Garg included in 1091 patients with ischemic stroke, by comparing artificial TOAST and deep learning machine automatic TOAST, found that the two effects are close, and automatic classification can avoid the difference of artificial judgment to some extent, which is of guiding significance for the future analysis of the etiology and classification of ischemic stroke [31]. Rehabilitation exercise can help patients recover their daily functional, and exercise relearning is an essential process for stroke patients. The Chinese Guidelines for Early Rehabilitation of Stroke also include exercise rehabilitation as one of the core contents of stroke treatment [32]. However, modern rehabilitation has the disadvantages of high-cost and unsatisfactory effect [33]. The operation only requires the patient to cooperate with the rehabilitation therapist and complete the daily rehabilitation training under his guidance, but we know that low-level central nervous injury in stroke patients needs to induce nerve remodeling through active stimulation of motor nerves, which is the key to the rehabilitation of stroke patients. However, traditional rehabilitation therapy not only consumes manpower and material resources but also lacks the process of active shaping of patients. Hang [34] used depth learning technology and focusing on the recognition method of human action posture, an online rehabilitation action recognition model is established, which can realize the supervision and guidance of human action in the process of rehabilitation training. The action recognition equipment of rehabilitation training for wearing stroke is widely used in Ma Gaoyuan [35]. The recognition accuracy can be as high as 92.86.

5. Application of Depth Learning in Stroke Prediction

Deep learning also has a long-term contribution to stroke disease prediction. The prediction of ischemic stroke has a decision-making effect on its treatment. According to Heo et al. [29], a total of 2604 patients with acute ischemic stoke were included to estimate their mRS scores three months after onset. Three machine learning algorithms were used: deep neural networks, random forest, and rosette regression algorithms compared with the register (ASTRAL) scoring method for acute ischemic stroke in Lausanne, Switzerland. The deep neural network model outperformed the ASTRAL score, and there was no statistically significant difference between the performance and the ASTRAL score of the random forest and logical regression model. In accordance with Bacchi et al. [36], the application of deep learning to predict radiologic outcomes after thrombolytic therapy for acute ischemic stroke revealed an accuracy of 0.74 for both NIHSS24 score ≥ 4 and mRs90 score 0-1. Ma et al. [37]. It is found that the segmentation quality of ischemic stroke by depth learning tool is equal to or higher than that of manual segmentation, and the volume of ischemic core is highly consistent, which can provide reliable information for ischemic stroke prediction. In view of the lack of accuracy in assessing the risk rating of stroke patients in the current model, Yang et al. [38] designed the prediction model of stroke risk grade based on the maximum edge of the deep neural network can integrate stroke data with too large interclass divergence, improve the accuracy of prediction, and enhance clinical practicability. Yao et al. [39] in view of the design and construction of the prediction model system for cerebrovascular diseases, and based on the applicability of long-term and short-term memory (LSTM) neural network to the medical system, a disease prediction model LSTM neural network is proposed. The model is effective. Chen et al. [40] proposed a stroke prediction method characterized by deep learning and Mel frequency cepstrum coefficient (Mel Frequency Cestrum Coefficient, MFCC). The MFCC language features are trained in the convolution neural network model to obtain stroke prediction results. Experimental results show that the accuracy of test set and training set is higher than that of logistic regression. Recent studies have shown that convolutional neural networks are more suitable for medical imaging data [41]. Chauhan et al. have studied a deep learning approach based on convolutional neural networks that can predict the severity of language disorders by 3D lesions MRI by stroke patients.

6. Outlook

Nowadays, the aging of society is increasing day by day. Stroke, as the first leading cause of death in chronic diseases, has far exceeded the severity of cardiovascular disease and caused a serious burden on society and family. Today, advocating AI empowerment and AI to good, DL has involved many fields, such as words, numbers, and images, among which the medical field has outstanding contributions. Deep learning in the imaging study of ischemic stroke can accomplish intelligent segmentation, focus detection, image analysis, prediction, and treatment of ischemic stroke images by exploring deeper image information, so as to reduce human error and greatly improve the work efficiency of clinicians. Its development is deepening, which provides a more effective solution for the rehabilitation of patients in the future. The flexibility of the deep learning model also provides a more valuable tool for the study of multimodal combination.

Although deep learning research is becoming more and more mature, it can liberate the hands of clinicians to a certain extent, but the small sample size is still the biggest drawback, and there is no more clinical trials. Nat Med released a new guide to welcome artificial intelligence clinical research in 2020 [42], in order to further standardize the depth of learning in clinical promotion. In addition, the DL big data lacks the sharing way, and in the future, domestic hope establishes the more perfect database sharing platform. Of course, we should not ignore the importance of raw data and deep mining to find its pathological pathogenesis. Deep learning should be further blended with the morphology of ischemic stroke to lay the foundation for intelligence, comprehensive assessment of the pathogenesis of ischemic stroke, and early warning of disease occurrence.

A large number of deep learning research have been widely carried out, still facing more challenges. As a bridge and interdisciplinary subject between medical workers, the innovation and development of deep learning are the fundamental basis of this research, which is particularly important under the background of fierce international competition. Therefore, interdisciplinary indepth research is the source of artificial intelligence youth vitality, for personalized, accurate, modern medicine that laid the foundation. It is believed that with the emergence of more excellent experimental designs based on clinical efficacy, the deep excavation of deep learning will be further advanced.

Data Availability

This article is a review article and does not contain relevant data.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of the paper.

Authors' Contributions

Miao Zhang and Siqi Zhang contributed equally to this work. Zhongren Sun and Tiansong Yang are both corresponding authors to this work.

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Research Article

The Effect of Applying Robot-Assisted Task-Oriented Training Using Human-Robot Collaborative Interaction Force Control Technology on Upper Limb Function in Stroke Patients: Preliminary Findings

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Stroke is one of the leading causes of death and the primary cause of acquired disability worldwide. Many stroke survivors have difficulty using their upper limbs, which have important functional roles in the performance of daily life activities. Consequently, the independence and quality of life of most stroke patients are reduced. Robot-assisted therapy is an effective intervention for improving the upper limb function of individuals with stroke. Human-robot collaborative interaction force control technology is critical for improving the flexibility and followability of the robot's motion, thereby improving rehabilitation training outcomes. However, there are few reports on the effect of robot-assisted rehabilitative training on upper limb function. We applied this technology using a robot to assist patients with task-oriented training. Posttreatment changes in Fugl-Meyer and modified Barthel index (MBI) scores were assessed to determine whether this technology could improve the upper limb function of stroke patients. One healthy adult and five stroke patients, respectively, participated in functional and clinical experiments. The MBI and Fugl-Meyer scores of the five patients in the clinical experiments showed significant improvements after the intervention. The experimental results indicate that human-robot collaborative interaction force control technology is valuable for improving robots' properties and patients' recovery. This trial was registered in the Chinese clinical trial registry (ChiCTR2000038676).

1. Introduction

Stroke is a common cerebrovascular disease that is diagnosed on the basis of clinical features and imaging [1]. Most strokes result from transient ischemic attacks associated with blockages of blood flow [2], while about 10–40% of strokes are attributed to intracerebral hemorrhage [3] caused by the rupture of cerebral arteries. Stroke remains the leading cause of death and disability in China despite substantial advances relating to its prevention and treatment [4]. More than 80% of stroke patients develop acute motor dysfunction, and almost 50% of patients eventually develop long-term motor function limitations [5]. Upper limb (UL) function is essential for executing daily activities. However, persistent UL sensorimotor impairments occur in up to 75% of stroke patients [6] and include paresis, ataxia, spasticity, a reduced range of motion spasticity, and poor spatiotemporal coordination, which significantly affect the quality of life of patients with stroke. Therefore, targeting UL function is a core element of rehabilitation to optimize patient outcomes and reduce disability [7].

Rehabilitation to improve and maintain patients' functions plays a critical role in the recovery process [8]. Many rehabilitative therapies have been applied to improve UL function, such as robot-assisted therapy [9], virtual reality [10], mirror therapy [11], music playing [12], transcranial direct current stimulation [13], motor imagery [14], bilateral motor training [15], task-oriented training (TOT) [16], and constraint-induced movement therapy [17]. Among these approaches, TOT [18] and robot-assisted training are reported to be effective for improving patients' poststroke abilities to execute activities of daily living (ADL) and their UL function [19]. TOT, which targets patient motor function control, entails applying physical training inputs within specific tasks associated with the patient's environment, while providing the patient with appropriate internal and external feedback. TOT can increase muscle strength on the hemiplegic side, correct a flawed compensatory strategy, and help the patient to establish a normal movement pattern [20]. It can simultaneously activate the corresponding expression area of the cerebral cortex and promote remodeling of the central nervous system in the corresponding functional area [21]. Robotic assistance, which enables highly repetitive, task-oriented, intensive, and quantifiable neurorehabilitation treatment to be delivered [22], is considered one of the most promising methods for functional UL restoration. A previous study found that a robot-assisted TOT program could improve the ability of stroke patients to grasp objects [23]. Though several studies have demonstrated the effectiveness of robot-assisted treatment, few studies have examined the application of human-robot collaborative interaction force control technology (HRCIFCT). This technology is critical for improving movement compliance, flexibility, and the followability of the robot's movements, which significantly enhances the effects of the inactive and assisted control modes of rehabilitative training.

We designed a robot-assisted TOT program centering on virtual reality games and entailing different levels of difficulty to improve the effectiveness of rehabilitative training. HRCIFCT was combined with robotic assistance, given its ability to improve the robot's properties, thus offering patients better service. This technology can solve the problem of dynamic compensation and enhance movement flexibility, while also accelerating the starting ability of the rehabilitation manipulator. Importantly, it can judge the patient's intended direction of movement, providing flexible tracking. All of these advantages contribute to making robot-assisted training more effective.

2. Materials and Methods

2.1. Type of Motion Training. In general, the type of motion training entailed in robot-assisted rehabilitative exercises varies according to the stage or severity of the disease. Three modes of motion training can be identified according to the auxiliary force provided by the robot: passive, assisted, and active motions. The passive mode of motion training is used to assist stroke patients who are unable to perform any kind of movement. The assisted motion mode is utilized to support stroke patients who can execute some kind of movement. Active movement encompasses the entire process of movement. Although it is fully self-initiated by patients, they are unable to complete the movement in a natural manner [24]. HRCIFCT entails a novel design and can significantly benefit patients who can perform an assisted or active movement. At the same time, TOT requires patients to have the ability to participate actively. Therefore, we focused solely on assisted and active modes of movement.

2.2. Rehabilitation System. The rehabilitation system used in this study was the FELXO-Arm1 system manufactured by Shanghai Electric GeniKIT Medical Science and Technology Co., Ltd. and comprises hardware and software components (Figure 1).

FELXO-Arm1 has five degrees of freedom, which is uncommon in rehabilitative therapeutic devices, and is used to help stroke patients recover UL function. It has three passive joints in the horizontal plane and two active joints in the sagittal plane, comprising a motor and gear, which could provide additional assistance to patients undergoing rehabilitative training. The encoder and the torque sensor have different functions. Whereas the former is used for recording angular measurements of joints, the latter is utilized to obtain human-robot interactive torque measurements. Different motion control algorithms can be developed based on the mechanical structure to enable its adaptation for different rehabilitative training modes.

The power unit on the sagittal plane of the joint, which comprises a Maxon EC motor and a Harmonic Drive harmonic gear, complies with the training requirement of robot-assisted UL rehabilitation. Additional 46 Nm and 13 Nm assistive torques can be used for the shoulder and elbow joints, respectively. In addition to the robot, this hardware system includes other components, such as the mechanical manipulator, a 3D force sensor, and a controlling computer.

The software for the motion rehabilitation system was developed by the same company running on the external computer system. To improve instantaneity and operability, the software was designed using a real-time module. It presents a variety of virtual reality games, which can be chosen for specific rehabilitation targets, such as improving the range of motion, cognitive function, and activities of daily living. The parameters of the games include background complexity, running speed, training time, and background music, and the level of difficulty can be set according to the requirements and capacities of different patients.

2.3. Human-Robot Collaborative Interaction Force Control Technology (HRCIFCT). Figure 2 presents a schematic diagram of the HRCIFCT, which comprises three parts: a UL rehabilitation robot (ULRR), the patient, and an interactive force control method. The ULRR provides three rehabilitation auxiliary training options, namely, passive, assisted, and active training, and the device is mainly applied in the active and assisted modes. According to the different torque values obtained, we determined that the ULRR could be used to assist patients undergoing active and assisted rehabilitative training. The angle sensor responds to information on the joint's motion in real time, and information on the interaction force between the patient and the ULRR is obtained through the torque sensor installed at the joint position.

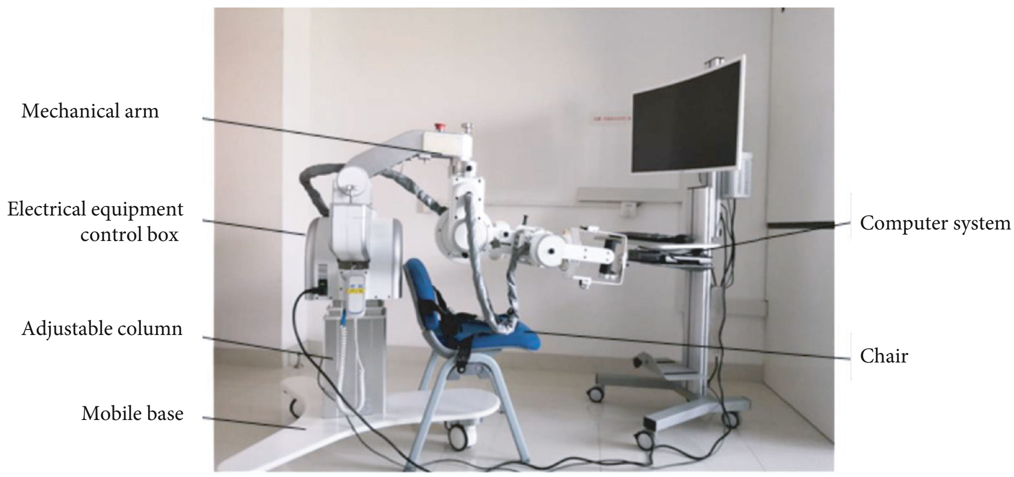

Figure 1: Robot-assisted rehabilitation system.

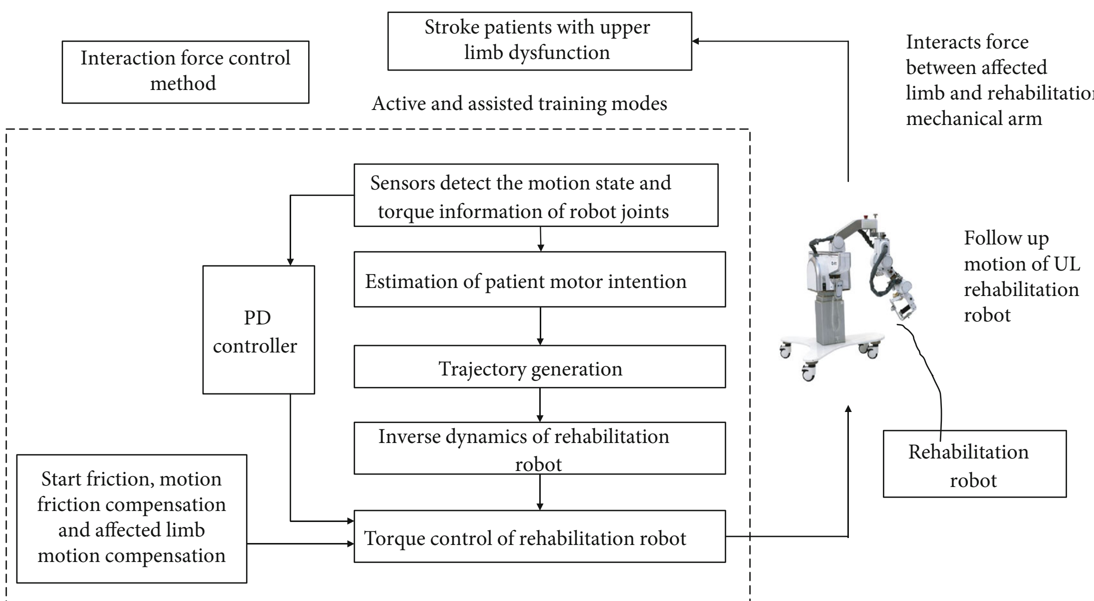

Figure 2: Human-robot collaborative interaction force and interactive control.

The interactive force control technology enables the patient's movement intention to be estimated. Using this technology, an inverse dynamic model of the ULRR arm, as well as the starting and kinematic friction and the motion compensation of the affected limb, can be established. Figure 3 presents a simplified model of the UL rehabilitation manipulator, depicting the arrangement of the two joints in the sagittal plane and the points of installation of the motor and sensor. The intended direction of movement can be determined according to the torque value detected by the joint torque sensor.

2.4. Task-Oriented Training for Assisted and Active Training Modes. TOT is a theory of rehabilitation characterized by divergence. Clinicians formulate a task to be implemented that is individually tailored to each patient according to their specific functional impairments and training targets. During the training session, the clinicians provide the patients with appropriate feedback, instructing them to maintain good posture and avoid compensation. Several studies have confirmed that a high number of repetitions performed within a single session yield better outcomes [25, 26]. To enhance therapeutic efficacy, the training tasks should be designed to intrigue the patient, thereby ensuring their continuous participation in the training program. Accordingly, we designed training tasks using different virtual reality games to demonstrate the efficacy of applying HRCIFCT to the UL function with robotic assistance.

2.5. Selection of Participants. We set the following inclusion criteria for selecting participants. (1) Patients were diagnosed with stroke, as confirmed by imaging and clinical data. (2) The diagnosis was confirmed less than 3 months after a stroke.

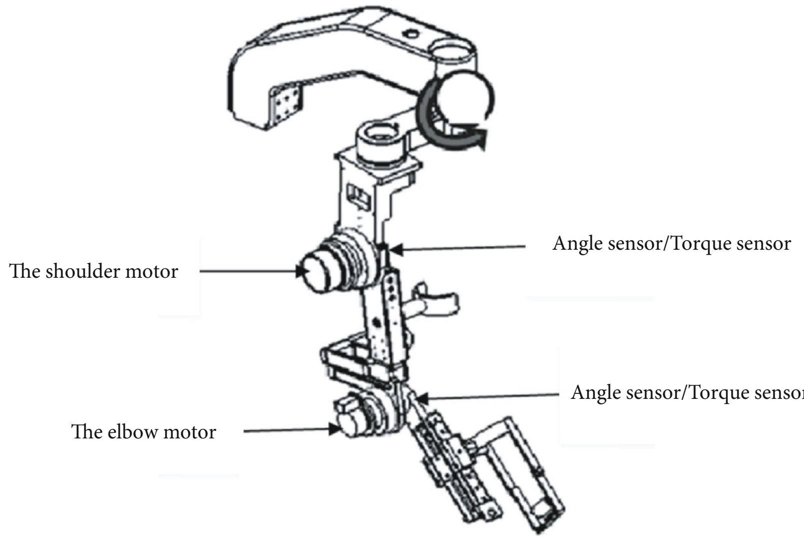

Figure 3: Schematic diagram showing the positioning of the motor and the sensor.

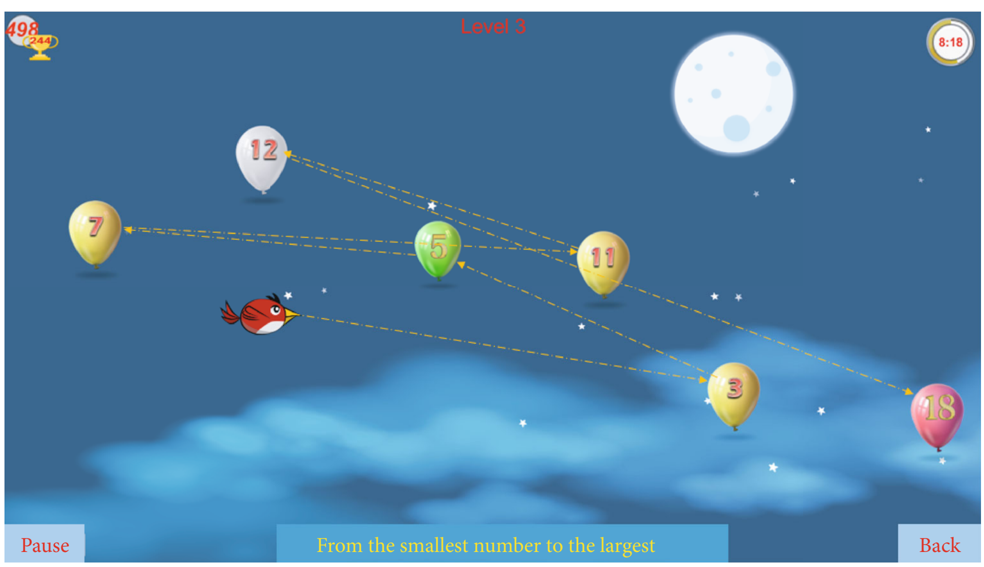

Figure 4: A schematic diagram of game-based task-oriented training.

(3) Patients exhibited mild to moderate motor impairment. (4) Patients exhibited mild spasticity of the affected UL (a modified Ashworth scale score < 2). (5) Patients agreed to participate in robot-assisted rehabilitative training.

The exclusion criteria were as follows: (1) orthopedic injuries of the musculoskeletal system, (2) severe visual or hearing impairments, (3) severe diseases of vital organs (e.g., heart failure or kidney failure), and (4) inability to complete the treatment. We also recruited a healthy volunteer for the functional experiments.

3. Experiments and Results

3.1. Experimental Scheme. In this study, the functional and clinical experiments were designed to test the effectiveness of the robot-assisted TOT. The training tasks comprised different virtual reality games. A healthy volunteer was asked to perform functional experiments after being instructed on how to use the robot and how to play the virtual reality game. Goals were used to test the practicability of the robot-assisted training system and the volunteer's subjective feelings while completing the task. In addition, five stroke survivors were recruited to participate in the clinical experiments, with the aim of testing the validity and utility of this rehabilitation system. Fugl-Meyer and MBI scores served as the primary measures.

3.2. Functional Experiments. The objective of the functional experiments was to test the robot-assisted rehabilitation system after incorporating the HRCIFCT to assess whether it elicited subjective feelings of comfort in the subject and

Table 1: Profiles of the stroke patients.

Patient code	Age (years)	Sex	Type of stroke	Days since stroke	Impaired limb	MMSE	Fugl-Meyer SEC	MBI
S1	66	Female	CI	16	Left	17	25	68
S2	63	Male	CI	65	Right	30	19	55
S3	56	Female	CI	61	Left	27	27	71
S4	75	Male	CI	71	Right	27	27	71
S5	68	Male	CI	62	Right	30	20	47

CI = cerebral infarction; MMSE = Mini-Mental State Examination; Fugl-Meyer (SEC) = Fugl-Meyer assessment for shoulder–elbow, coordination; MBI = modified Barthel Index.

provided efficient TOT. After all of the training preparations had been completed and the system had been connected, robot-assisted TOT was performed. One of the activities of daily living (ADL) training games was randomly chosen by a therapist who informed the volunteer about precautions to be taken. Two robot-assisted training modes, namely, assisted and active training, were then tested. Each model was tested continuously for 20 minutes using the same game. Figure 4 depicts the game content. During and after the training, we asked the volunteer about their subjective feelings. For example, during the assisted training, we asked the volunteer whether they could feel the auxiliary force exerted by the robot, whether this force was appropriate, and other relevant questions. We also asked the volunteer whether the game-based TOT was entertaining and likely to increase their willingness to participate. All of these issues are critical, as they influence patients' comfort and active participation during the training process and have a crucial bearing on patient outcomes. The subject reported a high level of satisfaction during the entire training process and confirmed that the software ran smoothly. Accordingly, we suggest that a robot-assisted rehabilitation system using HRCIFCT is effective in improving the UL function of stroke patients.

3.3. Clinical Experiments. The purpose of the clinical experiments was to validate the effect of robot-assisted TOT with HRCIFCT on the UL function of stroke patients during rehabilitation. Five stroke survivors were recruited as participants in the clinical experiments, which were held over a four-week period (more than three times per week for a total of 15 therapy days). Each survivor underwent one session of game-based, robot-assisted TOT that lasted 30 min on one therapy day. The patients also agreed to participate in two-hour daily sessions (5 days a week) that covered other interventions, including physical and occupational therapy according to the degree of their UL impairment and expectations. To evaluate the effect of robot-assisted TOT treatment on the recovery of UL function, the Fugl-Meyer shoulder and elbow coordination (SEC) and MBI scores were assessed. The UL function of the five stroke patients was evaluated before the treatment commenced, after the fifth treatment, and after the last session. Before participating in the experiment, all of the patients underwent a cognitive assessment using Mini-Mental State Examination (MMSE), which showed that it could accurately screen cognitive impairments and was clinically feasible [27].

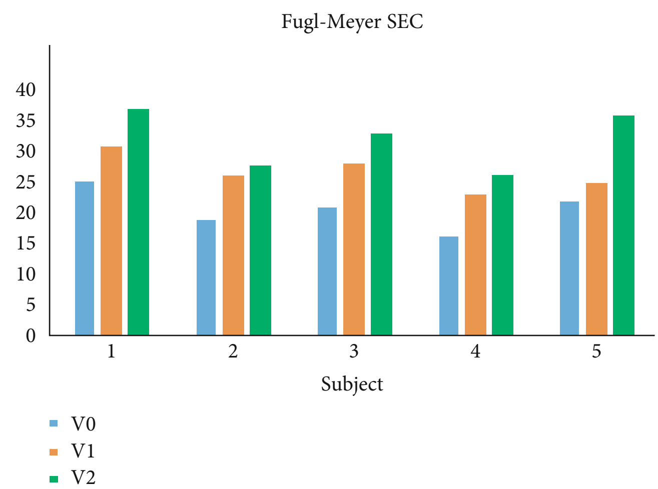

Figure 5: A comparison of the Fugl-Meyer SEC scores of stroke patients.

The Fugl-Meyer assessment, which measures the ability of individuals to move their affected UL, is a well-designed test that has been widely used in the stroke population worldwide and shown to be a valid and reliable measure [28]. The total score for UL function in the Fugl-Meyer assessment is 66. However, we adapted the test to focus on shoulder-elbow coordination and named this revised version Fugl-Meyer SEC. The maximum score for each item in the modified version was 3 points (with a maximum score of 42 points). The MBI is also widely used to assess the ability of individuals to perform daily activities [29]. It comprises 10 items, amounting to a total of 100 points. An evaluation of changes in pre- and posttreatment scores can be indicative of the treatment's effectiveness.

Table 1 presents the baseline demographics and clinical characteristics of the five stroke survivors. The number of days since stroke onset ranged from 16 to 71 days (a mean of 55 days) among the five patients. All five subjects had suffered cerebral infarctions, and the dominant sides of two of the patients had been affected. Three of the patients were men (a mean age of 68.7 years), and two were women (a mean age of 61 years).

After undergoing the robot-assisted TOT rehabilitation, all of the participants showed improvement in their shoulder-elbow coordination, as demonstrated by increases in the Fugl-Meyer SEC scores. After the fifth training session,

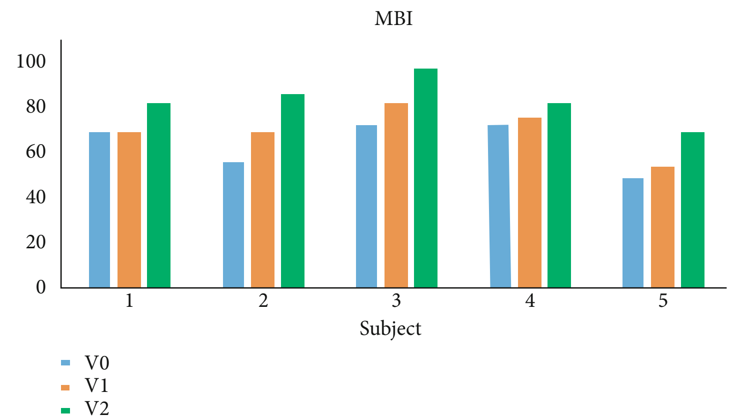

Figure 6: A comparison of the MBI scores of stroke patients. Notes: V0 denotes the initial value, V1 denotes the value after the fifth session, and V2 denotes the value after the last session.

the scores of patients 1, 2, 3, 4, and 5 increased by 5, 7, 7, 7, and 3, respectively. After the fifteenth training session, the scores of the patients increased by 12, 9, 13, 10, and 14 for subjects 1, 2, 3, 4, and 5, respectively. At the conclusion of the experiment, an increase in the score was most apparent for subject 5. Figure 5, which depicts the Fugl-Meyer SEC scores, reveals an upward trend in Fugl-Meyer SEC scores for the five subjects.

Similar to the Fugl-Meyer SEC scores, the MBI scores for the five patients also increased (Figure 6). Increases in the patients' scores for the second evaluation ranged from 0 to 13, being 0, 13, 9, 3, and 6 for subjects 1, 2, 3, 4, and 5, respectively. For the last assessment, increases in scores ranged from 10 to 30, being 13, 30, 25, 10, and 21 for subjects 1, 2, 3, 4, and 5, respectively. Of the five patients, only subject 1 did not achieve an increased MBI score in the second evaluation. However, in the last evaluation, the MBI score of subject 1 increased by 13 points. The MBI score of subject 4 increased by 10 points after completion of the treatment, which was the lowest increase among the five patients. Subject 2 showed the most dramatic increase, with a total gain of 30 points.

4. Discussion

With advancing technology, an increasing number of novel strategies are being developed and applied within clinical rehabilitation, bringing significant improvements to the UL function of stroke patients. Robots used in rehabilitation training are becoming increasingly critical for stroke patients [19] because they can provide a variety of targeted training modes for helping patients to recover lost or impaired functions. Previous studies have highlighted the importance of robot-assisted technology in the recovery of UL function [30]. TOT associated with motor relearning is widely used within rehabilitation programs and is being used to improve UL function [31]. To date, several TOT protocols have been developed to train patients, such as constraint-induced movement therapy, which is a specific TOT that can lead to enhanced motor function of the affected UL [32]. Using robot-assisted training combined with TOT is more efficacious than applying robot training on its own to improve the limb function of stroke patients [33]. Accordingly, we aimed to assess and validate the performance of robots when HRCIFCT was incorporated within a robot-assisted TOT program.

The results for the treatment outcomes of the five patients indicated that both the Fugl-Meyer SEC scores and the MBI scores showed improvements at the conclusion of the training program, although the MBI score of subject 1 showed no change after the second assessment. Moreover, scores obtained using both methods increased above the minimal clinically important difference (MCID). The MCIDs for the MBI and Fugl-Meyer assessments are 1.85 points [34] and 6.5 points [35], respectively. Therefore, we concluded that robot-assisted TOT incorporating HRCIFCT can be used as a safe and effective exercise protocol to improve the UL function of stroke patients. Some points require further discussion here relating the sites and time lapse following stroke onset among different patients. When interpreting these results, it is important to note that the five patients whom we selected were all in the early subacute phase of stroke (7 days to 3 months) [35]. Therefore, our interpretation only applies to stroke patients in this phase.

The Fugl-Meyer SEC score of subject 5 increased by 14 points after the final treatment. A possible reason for this increase could be the onset time of this patient (9 days). Studies have shown that early rehabilitative interventions are more effective than late interventions for restoring patients' functions and reducing the degree of disability. Despite the existing cognitive impairment of subject 1 (MMSE 17), this individual's posttraining Fugl-Meyer SEC score increased by 12 points. There are two possible reasons for this result. First, the duration of onset (16 days) for this patient was short, and second, the TOT centered on virtual reality games, which may be beneficial for improving cognitive function, as the results of a previous study also indicate [36].

Of the five patients, subject 4 showed the least improvement for their MBI score (10 points). Possible reasons for this result include the longer lapse between the stroke and treatment onset and a higher basal value, which resulted in just a small change in the patient's MBI score. Subject 2 showed the greatest improvement in their MBI score, amounting to 30 points after 15 sessions. A possible reason for this result is insignificant injury at the sites of the cerebral infarction in the brain stem and in the cortical spinal tract (CST), which is the key conduction tract that affects motor function. Significant damage to the CST can affect the performance and recovery of motor function [37]. Both the MBI and the Fugl-Meyer scores of subject 1 revealed progress after the training despite the patient's cognitive impairment. Therefore, we believe that patients with cognitive impairment will also have good therapeutic outcomes after receiving appropriate rehabilitative therapy.

5. Conclusion

The results of our experiments confirmed that robot-assisted TOT incorporating HRCIFCT can facilitate the recovery of stroke patients' UL function, even when cognitive dysfunction exists. Our findings also demonstrated that this robot-assisted rehabilitation system, entailing the application of HRCIFCT, is safe and effective. However, we conducted a small observational study; further research is required to confirm these results.

Data Availability

The data that support the findings of the study are available from the corresponding author on reasonable request.

Conflicts of Interest

All of the authors declare that they have no competing conflicts.

Authors' Contributions

Yingnan Lin has equal contribution as the first author.

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Review Article

Exploring the Use of Brain-Computer Interfaces in Stroke Neurorehabilitation

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With the continuous development of artificial intelligence technology, "brain-computer interfaces" are gradually entering the field of medical rehabilitation. As a result, brain-computer interfaces (BCIs) have been included in many countries' strategic plans for innovating this field, and subsequently, major funding and talent have been invested in this technology. In neurological rehabilitation for stroke patients, the use of BCIs opens up a new chapter in "top-down" rehabilitation. In our study, we first reviewed the latest BCI technologies, then presented recent research advances and landmark findings in BCI-based neurorehabilitation for stroke patients. Neurorehabilitation was focused on the areas of motor, sensory, speech, cognitive, and environmental interactions. Finally, we summarized the shortcomings of BCI use in the field of stroke neurorehabilitation and the prospects for BCI technology development for rehabilitation.

1. Introduction

According to WHO clinical criteria, stroke is defined as "a rapidly developing sign of focal (or global) brain dysfunction lasting more than 24 hours (unless interrupted by death), with no apparent nonvascular cause." Stroke is the world's second leading cause of death and third leading cause of injury and can cause severe cognitive, emotional, and sensorimotor impairment in patients [1]. Most stroke victims survive the initial event, and the greatest impact of stroke disease is usually the long-term effect it has on the patient and their family [2, 3]. Unfortunately, there are significant gaps between countries in the quality of stroke research and the effectiveness of medical interventions [4]. Over the last decade, advances in the medical treatment of stroke patients have resulted in a substantial reduction in mortality rates. However, one-third of the 16 million patients worldwide remain disabled each year [5].

In traditional rehabilitation, the gold standard in care for poststroke recovery is a combination of specialized training and general aerobic exercise. Bimanual arm training (BAT) and constraint-induced movement therapy (CIMT) are two of the most established methods for treating stroke-related sports injuries [6]. These rehabilitation techniques are bottom-up interventions that focus on distal limb modulation to cause subsequent improvements in the neural circuits involved in motor recovery. However, even with intensive task-specific training and physical activity, 15-30% of people who have had a stroke are permanently disabled. As a result, many bottom-up interventions are ineffective in stroke patients who have very limited upper limb mobility (Fugl-Meyer score 20) [7]. We need to explore and develop more effective stroke rehabilitation strategies that supplement or replace traditional rehabilitation training.

The remodeling of neurological function after stroke may facilitate the development of new interventions for

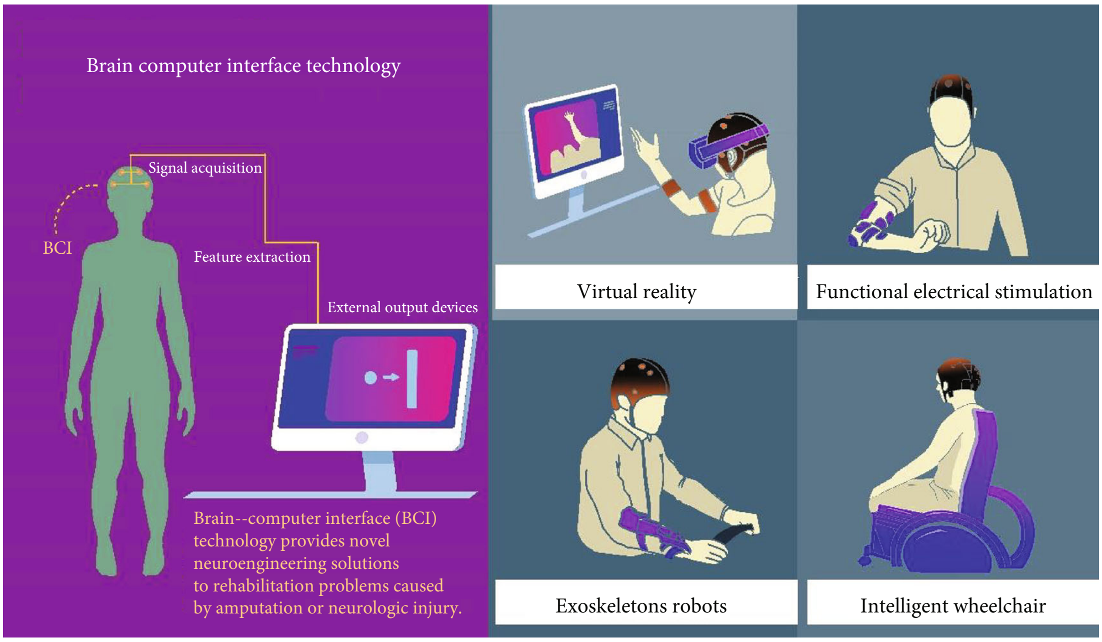

Figure 1: Brain-computer interface for the acquisition, extraction, and conversion of signals from the brain for the ultimate application of controlling external devices: virtual reality, functional electrical stimulation, exoskeleton robots, and intelligent wheelchairs.

poststroke rehabilitation, and recent therapeutic options have shifted to facilitating neural circuit reorganization in order to restore motor function. These top-down approaches to rehabilitation are largely due to the mechanisms of brain plasticity [8]. The advancement of artificial intelligence methods and a better understanding of brain plasticity are also critical for functional movement recovery. The human brain's ability to adapt to change and environmental stimuli (brain injury, treatment, and experience) by reorganizing its structure, function, and connections is known as brain plasticity [9]. The basic structural reserve and anatomical plasticity of the brain are important parameters for significant motor recovery [10]. Therefore, the key challenge is to figure out how to optimize neuroplasticity during treatment while also reinforcing connections across the infarcted region and promote creation of new connections, thus facilitating long-term functional recovery.

With the advancement of science and technology, artificial intelligence technologies, such as brain-computer interface (BCI), virtual reality (VR), and augmented reality (AR), are rapidly developing and are gradually being applied in the field of medicine. Due to its direct action on the brain, BCI induces brain plasticity and promotes functional reorganization of the brain, proving to be a superior approach in poststroke rehabilitation, especially for improving motor function in stroke patients. The limited neurorehabilitation modalities are no longer adequate to meet increasing rehabilitation needs of patients with central injuries, and BCI has been shown to be effective in improving motor function and enhancing the lives of stroke patients. In this review, we first examined the latest BCI technologies, including how BCIs are acquired, how signals are processed, and how other artificial intelligence technologies are combined with BCIs, such as functional electrical stimulation (FES) technology, virtual reality, exoskeletons, orthotics, and intelligent wheelchairs. We then presented the specific applications, mechanisms of action, and efficacy of BCI in the treatment of poststroke neural remodeling, such as in BCI-based neurorehabilitation of stroke patients in motor, sensory, verbal, cognitive, and environmental interactions. Finally, we summarized our recent research findings and shortcomings, as well as an outlook on the development of BCI technology in the field of rehabilitation.

2. BCI Technology

The word "brain-computer interface" was first formally identified as "a communication device that does not depend on the usual output pathways of the peripheral nerves and muscles of the brain" at the First International Conference on Brain-Computer Interface Technology in June 1999 [11]. The brain-computer interface (BCI) is a new technology that enables interaction with one's environment through brain signals. This technology takes physiological measurements of mental states directly from the brain and converts them into control signals that can be used to control external devices or computers [12]. The BCI recognizes a set of patterns in brain signals by going through four successive stages: signal acquisition, feature extraction, feature transformation, and device output [13] (Figure 1).

2.1. Signal Acquisition Techniques. A BCI uses signals from the brain to gather information about the user's intentions. To do this, the BCI relies on a recording phase to measure brain activity and will then convert that information into an electrical signal that can be easily processed. Depending on the BCI's level of invasiveness, there are two types of recording methods: invasive and noninvasive. Invasive recording methods have more spatial and temporal precision, but they also come with the dangers that come with surgically implantable instruments. Extensive research into noninvasive recording techniques has quickly increased due to the technique's noninvasive and safe nature. Due to the low quality of collected signals and susceptibility to interference, enhancing the signal quality of noninvasive brain-computer interfaces has become a focus of research. Depending on the form of signal acquisition, noninvasive BCIs are divided into electroencephalography (EEG), electrocorticography (ECoG), magnetoencephalography (MEG), intracortical electrical signal mapping (INR), near-infrared spectroscopy (NIRS), functional magnetic resonance imaging (fMRI), and many more. The classification of these acquired signals relies on two types of brain activity: (I) electrophysiological and (II) hemodynamic. These neural signal acquisition methods differ mainly in terms of activity detection, temporal and spatial resolution, safety, and mobility [14] (Table 1).

2.2. Feature Extraction. The BCI operation's signal processing phase is split into two sections. Feature extraction is the first step, which extracts the signal features that encode the user's purpose. Different types of thought generate different patterns of brain signals, and the BCI classifies each pattern into a category based on their characteristics. Depending on the type of control signals in the BCI, the patterns can be divided into visual evoked potentials (VEPs), slow cortical potentials (SCPs), P300 evoked potentials (P300), or sensorimotor rhythms (μ and β rhythms). In this step, the digitized data is algorithmically filtered to remove confounding artifacts, such as 60 Hz noise or EMG activity, to ensure accurate measurements of brain signal characteristics [13].

2.3. Feature Translation. The second step in signal processing uses a conversion algorithm that converts extracted signal features into system commands. Brain electrophysiological features or parameters are converted into commands that will generate outputs, such as letter selection, cursor movement, and regulation of a motorized prosthetic, and influence additional assistive devices. The conversion algorithm must be dynamic to accommodate continuous changes in signal characteristics and ensure that the range of the user's specific signal characteristics fully covers the range of control for the device [14].

2.4. External Output Devices. End effectors are external output devices that are operated by BCI commands. The function and design of these devices vary depending on the intent of the BCI system and the needs of each end user. Here, we will focus on motor control and neurorehabilitation as end effector targets for BCIs, including functional electrical stimulation (FES), VR, intelligent wheelchairs, orthotics, and exoskeletal robotic devices.

2.4.1. BCI-FES. Functional electrical stimulation (FES) technology works by sending electrical impulses to a paralyzed or damaged limb in order to produce artificial muscle contractions [15]. The benefits of BCI-FES therapy include the ability to promote functional recovery and purposeful plasticity by activating the body's natural efferent and afferent pathways, thereby facilitating motor learning and neural reorganization [16]. One study showed the additional psychological advantages of rehabilitation using BCI-FES with patients, such as increased self-esteem and reduced depression [17]. Another study showed that BCI-FES-treated stroke patients performed skilled and coordinated grasping, made clinically significant progress on tests of upper limb function, and showed improved shoulder subluxation [18]. A new technology, sensory-motor rhythm (SMR) based BCI-FES system, combines the benefits of both technologies, allowing patients with severe disabilities to regain motor function by converting random motor imagery (MI) into physical movements [19]. An enhanced MI-BCI system based on FES and VR has been proposed and validated, unveiling a new era of intelligent rehabilitation therapy [20].

2.4.2. BCI-VR. In recent years, BCI combined with VR technology has become a new technique that has significant applications in neurorehabilitation. Compared to traditional rehabilitation methods, BCI-VR systems can improve individual motivation by increasing the appeal of training, thus shortening the training cycle, providing more effective feedback, and facilitating recovery of brain function [21]. Badia et al. showed that the use of BCI-VR systems could monitor and facilitate cortical reorganization through motor training [22]. Vourvopoulos et al.'s research has shown that a BCI-VR system based on the Reinvent platform can be extremely helpful for patients with severe movement disorders and that the system can be used repeatedly by patients undergoing stroke treatment [23]. A study by Laver et al. also suggests that VR may be beneficial when used as an adjunct to daily care to increase overall treatment time and in turn improve upper limb function and patient autonomy [24]. However, the combination of BCI and VR is only in its infancy, and the current information transfer rates of BCI systems are not ideal. There still remains a long way to go before this technology can be effectively applied to the rehabilitation of patients with neurological diseases.

2.4.3. Orthotics, Exoskeletons, Robotics, and Intelligent Wheelchairs. The main considerations of exoskeletal and orthotic devices for stroke patients are rehabilitation and replacement. An orthotic supports a joint as it moves from static to functional position and can also generate dynamic movements through the range of motion of the joint. This method is useful for patients with low motor neuronal disease or severe muscle atrophy. Ramos-Murguialday et al. developed a new combined EEG-EMG-based BCI technology for use in a BCI-operated hand orthotic neurorehabilitation system, and this technique has thoroughly demonstrated superiority over traditional cortical muscle coherence-based BCI classifications [25]. An et al. have made considerable progress in the application of the BCI-Rogo system to gait orthotics; the combination of behavioral activation of the supraspinal gait region by BCI with the central spinal gait pattern generator via Rogo feedback drive may provide a unique form of Hebbian learning [26, 27]. Rohm et al. developed a hybrid system, which consisted of the FES system and

Table 1: Comparison of BCI pivot signal acquisition methods and their advantages and disadvantages.

Nerve-signal acquisition methods	Event monitoring	Time resolution	Spatial resolution	Safety	Advantage	Disadvantage
Electroencephalogram (EEG)	Electrical signals	~0.05 s	~10 mm	Noninvasive	High temporal resolution, relatively low cost, high portability, low risk to users	Poor signal quality
Magnetoencephalography	Magnetic signals	~0.05 s	~5 mm	Noninvasive	High temporal and spatial resolution, less training time, and more reliable communication	Technology is too large and expensive
Electrocorticography	Electrical signals	~0.003 s	~1 mm ~0.5 mm (LEP)	Invasive	High temporal and spatial resolution and low artefact vulnerability	Electrode mesh implanted in craniotomy, harmful to health
Intracortical point signal acquisition	Electrical signals	~0.003 s	~0.1 mm (MUA) ~0.05 mm (SUA)	Invasive	High spatial and temporal resolution	Signal quality and sensitivity diminish with time
Functional MRI	Metabolism	~1 s	~1 mm	Noninvasive	High spatial resolution	Very low time resolution, too large to carry
Near-infrared spectroscopy	Metabolism	~1 s	~5 mm	Noninvasive	Low cost, high portability, and acceptable time resolution on the order of 100 milliseconds	Very low spatial resolution

a semiactive orthotic, which restores hand, finger, and elbow function in tetraplegic patients; sustained training with this system can also reverse severe wasting atrophy of paralyzed muscles years after the initial spinal cord injury [28].

Robotic exoskeletons offer the advantages of increased joint strength and reduced load-bearing. Exoskeletons allow soldiers to lift heavy objects and can assist firefighters who have to wear heavy equipment. At the same time, exoskeletons can be utilized to assist the elderly or people with motor impairments in their daily activities. Combining these advantages with BCI technology, the exoskeleton-BCI system can enhance rehabilitation by providing the ability to repeat training exercises to increase the intensity of movement [29]. Bundy et al. demonstrated the effectiveness of a home-used BCI-controlled exoskeleton on motor function in chronic stroke survivors and found a potential correlation between the unaffected cerebral hemisphere and functional recovery [30]. For people with paralysis, restoring unrestrained mobility is another important issue that needs to be addressed. As a result, BCI-driven wheelchairs have become a quickly growing area of research and development. For example, Bundy et al. developed an EEG-based electric wheelchair that detects directional commands via EEG then uses them to directly control the wheelchair. However, more precise handling is more demanding on the user [30].

There is a desire to harness the potential of BCIs to transform the recovery process from neurological disease. Although it is still too early to apply the brain-computer end effector interface in a clinical rehabilitation setting, there has been significant progress in the integration process. Next, we will elaborate on BCI technology and its application in neurorehabilitation after stroke.

3. BCI Applications in Nerve Rehabilitation after Stroke

The use of BCI in stroke neurological rehabilitation is a new attempt in modern rehabilitation. Among them, the functionality of BCI in the remodeling of stroke patients' central nervous systems is a pressing topic of inquiry. Neuroplasticity refers to the process by which the brain learns new behaviors, adapts to the environment, and modifies behavior by adding or changing existing synapses. The Hebbian theory, developed by Canadian cognitive psychologist Donald Hebb (1904-1985), suggests that repetitive stimulation of postsynaptic neurons by presynaptic neurons enhances the efficacy of synaptic transmission [31]. Therefore, the aiding technology must match the patient's motor intentions in order to work optimally. In contrast to conventional rehabilitation tools, BCIs can use analysis by exogenous output devices to transform electrical signals from the brain into corresponding commands, thus enabling interaction between the brain and external environment [32]. The brain-limb linkage of hemiplegic patients has greatly increased the motivation of patients, changing from passive acceptance of conventional rehabilitation to active participation in training, which improves the effectiveness of rehabilitation. The replacement and regeneration of impaired neurological function are two essential functions of BCI in recovery [8]. As BCI systems are used to replace missing neurological functions, the user's ability to communicate with and monitor a range of environments and behaviors is restored, including computer-based tasks (word processing, Internet searching, and so on), accessibility devices (powered wheelchair drives) [33], neuroprosthetics [34, 35], and orthotics [25–28]. By inducing activity-dependent brain plasticity, BCI can be used in combination with recovery therapy to help restore normal central nervous system function (Table 2).

3.1. Motor Rehabilitation. Long-term motor disability as a result of stroke is one of the main targets of rehabilitation [36]. Even with traditional rehabilitation methods, over two-thirds of survivors develop mild to severe paralysis of the upper and/or lower limbs [3, 37]. It is estimated that nearly 1% of the world's population lives with the sequelae of cerebrovascular events [38]. Impaired motor control [39], general cognitive deficits [40–42], difficulties with speech production or processing [43], and altered mood states [44] are common debilitating effects of stroke [45]. For patients with poststroke motor dysfunction, rehabilitation interventions fall into two categories. The first type is the direct input of externally generated stimuli into the brain (transcranial direct current stimulation, transcranial magnetic stimulation, etc.), and the second type is training for the peripheral limbs. For these purposes, innovative technology-based solutions such as robot-assisted therapy, virtual reality, FES, noninvasive brain stimulation (NIB), and BCI have been suggested [46].

The restoration of upper limb motor defects in serious stroke patients was the initial impetus for the investigation of BCI technology in the field of poststroke rehabilitation. Patients with severe injuries do not have the minimum motor capacity required to undergo traditional rehabilitation therapies, such as occupational therapy (OT) or constraint-induced movement therapy (CIMT), which necessitates the search for a new kind of rehabilitation intervention [45]. The discovery that imagining movement (MI) causes the recruitment of the same neuronal circuits as real movement suggests that BCIs may be useful in recovery. The primary motor cortex (M1) and other brain structures involved in planning and regulating voluntary activity have been shown to be activated by motor imagery [47–50]. For example, studies have shown that motor imagery of clenched fists lowers the threshold of excitation for motor evoked potentials (MEPs) induced by transcranial magnetic stimulation (TMS) delivered to M1 [49]. Numerous studies have shown that BCI treatment can trigger long-term neurological changes and improve upper limb motor function in patients with subacute and chronic strokes [16, 51–57]. Ang et al. published the first report on observed clinical improvement, demonstrating that a BCI-supported robotic rehabilitation system based on motor imagery can improve upper limb motor function in stroke patients and facilitate rehabilitation of the affected hand and wrist in poststroke patients [53]. Eight of the chronic stroke patients had their upper limbs rehabilitated using a

Table 2: Current state of the application of BCIs in the field of stroke rehabilitation.

Current state of the development of BCIs in the field of stroke rehabilitation	
Motor rehabilitation	The use of BCIs is rapidly developing in the field of locomotion, and BCIs are effective in restoring upper and lower extremity motor when used in conjunction with FES, robotics, and robotic arms.
Sensory rehabilitation	Related research is working on sensory-motor modalities for BCIs, and the development of sensory-motor closed-loop systems will improve the efficiency of rehabilitation. However, the development of sensory rehabilitation is still in its initial stage and has not yet been put into clinical use.
Communication rehabilitation	BCIs can not only help restore the rehabilitation of language disorders in stroke but also serve as a substitute for language to restore the ability to communicate in patients with language loss. Currently, the study is based on three main signals: SCP-BCI, SMR-BCI, and P300-BCI.
Cognitive rehabilitation	Applying BCIs to cognitive training improves certain cognitive functions in neurodevelopmental and neurodegenerative diseases, but there are relatively few clinical studies.
Environment interaction	The application of BCIs in environmental interaction is the most humane consideration for the quality of life of stroke patients with hemiplegia. The development of smart homes is greatly increasing interactions between patients and the outside environment.

BCI. By pushing the damaged hand outwards with the MIT-Manus robot, the BCI device successfully detected MI from real-time EEG signals, based on the MI protocol. On the Fugl-Meyer Assessment Scale, major changes in motor control were reported after 12 recovery sessions over a four-week span (FMA). In 2003, Pfurtscheller et al. [58] were the first to use BCI in combination with FES to enable a tetraplegic patient to grasp a cylinder with his paralyzed hand. Caria et al. showed significant improvement in arm and finger motor function after four weeks of magnetoencephalography-based BCI combined with finger flexion and extension bracing, as well as improvement in a patient in a chronic phase of stroke with severe hand paralysis, using only four weeks of EEG-BCI-robotic arm training [59, 60]. Daly et al. [61] reported in a case of a patient that, after three weeks of BCI-FES training, the affected hand went from having no individual finger separation and no finger extension ability to achieving some degree of independent extension of the index finger.

Taylor et al. performed BCI-based interventions on healthy individuals and stroke patients and recorded motor-related cortical potentials by EEG during MI and ankle dorsiflexion in these subjects, demonstrating that BCI training can affect motor cortical excitability in the lower limbs of both healthy adults and stroke patients [62]. Chung et al. [63] utilized BCI combined with FES for ankle dorsiflexion in stroke patients (observation group) and only FES for ankle dorsiflexion in the control group. After five days of continuous treatment, there was a significant improvement in the standing and walking time test, as well as gait and stride length, in the observation group, while there was no significant improvement in the control group. BCI-based FES training is therefore considered to be more effective than FES alone in improving balance and gait function in stroke patients. Available evidence suggests that BCI training has a significant and immediate effect on improving limb motor function. However, the limited number of studies available does not provide evidence regarding its long-term impact. A large number of clinical trials and the development of new systems must be the focus of the future of motor rehabilitation [64] (Table 3).

Table 3: Sports rehabilitation author statistics.

Author	BCI facility	Site of action	Result
Ang	BCI-robotic	Upper limb	Improvement
Pfurtscheller	BCI-FES	Hand	Improvement
Caria	BCI-robotic	Arm and finger	Improvement
Daly	BCI-FES	Hand and finger	Improvement
Taylor	BCI-orthotics	Lower limbs	Improvement
Chung	BCI-FES	Ankle	Improvement

3.2. Sensory Rehabilitation. While BCIs have made great strides in motor control, significantly less attention has been paid to restoring tactile or skin sensation [65]; haptics is essential for many aspects of motion control [66]. When performing tasks that involve dexterity, such as lighting a match or finding a key, sensory input becomes even more important [65]. Our brains do not separate sensory and motor functions; instead, they construct complex motor strategies and equate desired results to sensory input to make necessary changes. These BCIs will need to combine motor and sensory modalities in order to truly restore function to the arm and hand. Despite the fact that sensory and motor cortices are located in separate anatomical areas, they share the same somatic organization and a critical functional relationship. It should also be remembered that complex and smooth limb movements depend heavily on the incorporation of sensory data to allow for the dynamic adjustment of multiple movement states at the same time [67]. Without tactile signals, our dexterity in grasping and manipulating objects would be severely impaired [68, 69]. Reduced sensory input makes tasks like ascending stairs and walking on uneven ground with a prosthesis challenging, if not risky, for lower limb amputees [69]. Studies on nonhuman primates have shown that the sensory stimulation of closed loops improves motor BCI performance [70]. A promising, recently developed technology now exists that can restore sensorimotor function using a robotic arm controlled by a BCI [66]. However, there is currently no technology available to restore motor function and tactile sensation using the participant's own hands [71–

73]. The establishment of bidirectional BCIs on "closed-loop systems" is therefore a new direction for future research to explore.

3.3. Communication Rehabilitation. Speech production and communication comprehension deficits afflict up to 30% of people who have had a stroke [74]. Today, the development of BCI technology may be beneficial for the rehabilitation of patients diagnosed with aphasia [75]. Brain-computer interface technology can not only provide a tool for communication but also support neuronal plasticity by activating language circuits, thereby facilitating recovery from aphasia. Three EEG signals for common language communication have been developed alongside EEG-based BCIs and studied: slow cortical potential (SCP), sensorimotor rhythms (SMR), and P300 evoked potentials (P300) [76]. Chaudhary et al. demonstrated for the first time the feasibility of SCP-BCI communication with two locked-in state (LIS) patients diagnosed with amyotrophic lateral sclerosis (ALS) [76]. Lazarou et al. showed that after six months of training, the participant successfully self-regulated his SCP by producing two different brain responses. In the end, he managed to write 454 words in German [77]. Sellers et al. made good progress using noninvasive P300-BCI to rehabilitate communication in LIS patients as well [78]. Kleih et al. applied P300-BCI to five participants diagnosed with poststroke aphasia for communication rehabilitation; participants successfully learned to communicate using a speller with an accuracy rate of 100% [75].

3.4. Cognitive Rehabilitation. People who have had a stroke also often suffer from cognitive impairment. Cognitive impairment can be seen as a range of deficits, including poor concentration, slowed information processing, memory impairment, reduced semantic fluency, difficulty producing or processing speech, and aphasia [45]. Most treatments, including motor rehabilitation based on brain-machine interfaces, require a certain minimum level of cognitive ability for the patient to be able to understand and respond to instructions for implementing the rehabilitation program [53, 79, 80]. Patients with severe cognitive impairment who are not capable of meeting these cognitive requirements are automatically excluded from rehabilitation, resulting in a significant reduction in quality of life. Therefore, making most poststroke rehabilitation programs accessible to all patients may be an important facet of cognitive training to consider. Cognitive rehabilitation is defined as a systematic, functionally oriented service of therapeutic activities. The assessment and understanding of the patient's brain behavioral deficits are assessed across many cognitive domains: attention, concentration, memory, comprehension, reasoning, problem solving, judgement, planning, self-monitoring, awareness, and more [81]. Surprisingly, despite the fact that motor function has received a lot of attention in BCI-based rehabilitation and BCIs have shown a lot of promise in promoting motor rehabilitation, there is still a lot of research on using BCIs for poststroke cognitive training [82, 83].

The effects of neurofeedback training based on BCIs have been shown to improve certain cognitive functions in neurodevelopmental and neurodegenerative disorders, such as attention-related hyperactivity disorder (ADHD) [84] and mild cognitive impairment (MCI) in the elderly [85]. Thus, spatially directed enhancement of self-regulation in cortical areas may be another method that can be used for cognitive training. A recent meta-analysis also showed encouraging evidence from several studies demonstrating the effectiveness of neurofeedback-based cognitive training [86]. Gomez-Pilar et al. developed a neurofeedback training (NFT) tool for BCIs based on motor imagery. After NFT training, three cognitive features, visual perception, articulate expression, and immediate memory, all improved dramatically [81, 87]. Martin et al. developed an online cognitive rehabilitation application based on the P300-BCI system for the remote treatment of patients with traumatic brain injury, in conjunction with therapists who will use the BCI at home. This allows therapists to remotely prescribe activities of varying difficulty and offers hope for recovery for people with severe physical and cognitive impairments after a stroke [81]. Furthermore, changes in cognitive outcomes after a stroke can have a concomitant impact on motor function and recovery outcomes. There is a correlation between cognitive and motor function and recovery outcomes, according to several studies [88].

3.5. Environmental Interactions. In the technical development of BCI-smart home control systems, the majority only consider younger healthier target populations. However, elderly people with disabilities or limited mobility are more interested in or in higher need of smart homes because of their limited capabilities; being able to operate household appliances at home on their own would greatly enhance their quality of life [89]. BCIs can be used in many different fields: medical applications to control wheelchairs and prostheses [12] or enable people with disabilities to communicate and write texts [90] and general public applications to control toys, video games, or general computer applications. Kosmyna et al. conducted a study using BCIs for the control of smart homes and found that healthy subjects achieved a 77% accuracy on the task given; however, better accuracy was obtained by subjects with disabilities (81%). It was concluded that disabled end-users are more motivated to learn to use the BCI correctly and that the use of BCIs for smart home control is feasible, but further research is needed [89]. Tang et al. developed a brain-driven intelligent wheelchair system that was tested in three patients (cerebral infarction, spinal cord injury, and stroke) and four healthy subjects. Tasks required the user to drive the system close to a walking person and talk to them, to pass through a door into another room, and to pick up a bottle of water on a table and drink it. The results show that the system operates with flexibility and efficiency, with users only needing to issue small commands to receive attentive service. Additionally, it shows that the system is important in accelerating the use of BCIs in real-world settings, particularly for patients using them during rehabilitation [91]. Current wheelchairs, exoskeleton technology, and other smart home developments must continue to be designed to support older or disabled people so that they can continue their daily lives, while also supplementing rehabilitation of deteriorating muscle and motor functions.

Smart home environments can ultimately help older people to live independently and feel safe in their own homes.

4. Discussion

With the rapid development of modern technology, brain-computer interface (BCI) technology has become an extremely relevant topic in research, and the application of BCIs in the medical field has become one of the more important reasons encouraging its development. While this novel treatment for neurological rehabilitation after stroke is proving to be extremely beneficial, there are a number of areas that need improvement in the field of BCI research. The first area to address is the development of bidirectional BCIs. While we have currently made great progress in BCI motor control, we are at a distinct disadvantage for the recovery of tactile or cutaneous sensation, where the recovery of a limb requires the integration of both motor and sensory modalities. This is where a combination of a bidirectional BCI and a "closed-loop system" that integrates both motor output and sensory input is appealing, where the motor output is adjusted based on the sensory input to achieve the optimal motor route. A neuroprosthetic based on a bidirectional BCI is already under development, and it is just a matter of time until it is applied to stroke neurorehabilitation to better guide clinical practice. The second area that needs to be examined is the application of synchronous versus asynchronous BCI. The stroke BCI rehabilitation systems introduced in this paper, robotic arm, VR, and intelligent wheelchairs, are all synchronous BCI. A synchronous BCI system requires the user to set the EEG data acquisition experimental paradigm to obtain time-specific, real-time acquisition of data; therefore, the user is always "working" in sync with the system. In practice, however, users cannot be in a "working" state for long periods of time, and in most cases, they are usually in a "free" state. In order to improve the usability of online systems and avoid various errors, it is necessary to identify this idle state; to address this need, asynchronous BCIs have been created. There are studies on asynchronous BCI systems, but few of these regard applications to clinical rehabilitation. Asynchronous BCI movements would truly give patients full autonomy in their rehabilitation. Another exciting future possibility is the hybrid brain-machine interface, which requires the use of EEG as well as other physiological signals, such as neuromodulation (noninvasive brain stimulation), electromyographic activity, and heart rate, as input. These combinations can work synergistically to make the control algorithm more robust and to improve the reliability of the user's intent to detect. For example, the existing BCI-robotic arm rehabilitation system only relies on EEG to drive the paralyzed limb in rehabilitation, and there is no active movement of the limb at all. However, under hybrid BCI control, we can use both EEG and EMG to jointly control the manipulator's arm and enhance the "shared control" of the effector's devices. Shared control between the preprogrammed control of the end effector device and the neural control of the human brain-computer interface has potential to improve the performance of motor tasks. Another phenomenon that must be explored is how the quality of signal acquisition of the BCI system directly determines the degree of execution of the effector. In terms of the current classification of signal acquisition methods, there are two types: invasive and noninvasive. Invasive BCI has the advantage of good signal quality, but the disadvantages are that it is very invasive and degrades over time due to damage to the electrode sheet. We therefore need to develop harmless, more stable electrode materials. The advantages of noninvasive BCI are its safety and convenience, but the disadvantage is its poor signal quality. We need to balance the advantages and disadvantages of both devices to find a more efficient way of collecting signals and to continue developing intelligent adaptive neural interfaces.

5. Conclusion

This review describes several BCI applications (e.g., motor, sensory, verbal, cognitive, and environmental interactions) to aid in the rehabilitation of stroke patients. We hope that the techniques presented in this paper will further contribute to the design of new applications and devices for BCI-based stroke rehabilitation. Brain-computer interface technology has already demonstrated exciting results in providing cognitive and physical support and rehabilitation, and we look forward to future innovations in this important area of research that will ultimately affect us all.

Data Availability

This article is a review article and does not contain relevant data.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of the paper.

Authors' Contributions

Tiansong Yang and Xiaowei Sun contributed equally to this work. Siyu Yang and Ruobing Li are first authors.

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Review Article

The Effect of 3D Printing Metal Materials on Osteoporosis Treatment

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3D printing has been in use for a long time and has continued to contribute to breakthroughs in the fields of clinical, physical, and rehabilitation medicine. In order to evaluate the role of 3D printing technology in treating spinal disorders, this paper presents a systematic review of the relevant literature. 3D printing is described in terms of its adjunctive function in various stages of spinal surgery and assistance in osteoporosis treatment. A review of metal 3D printed materials and applications of the technology is also provided.

1. Background

3D printing technology works by applying computer design software to rapidly collect bondable materials and print them layer by layer in order to create a solid 3D model. 3D printing technology has improved dramatically since its launch in the 1990s. Although originally used in industry, the idea of "Bio-Manufacturing" with 3D printing was introduced in the late 1990s, and the technology started to be applied in the medical industry [1]. Because of its high accuracy and complexity, it has been used in orthopedic clinics to develop solid bone models, auxiliary materials for orthopedic surgery, and bone tissue replacements (implants) [2]. The spine is a complex but vital structure in the human body, with a variety of morphologies. Thus, doctors have used 3D printing technology to build spine models, intravertebral implants, guidance templates, and rehabilitation supports to increase the precision and recovery rate of spine surgery.

2. Application of 3D Printing Technology in Spinal Surgery

2.1. Basic Teaching. Any surgeon in the field of spine surgery needs to have a strong background in anatomy. Medical education is being aided by 3D printed spine models. 3D printed spine fracture models can help physicians identify complex spine fracture markers, practice prior to spine surgery, and develop standardized training programs [3, 4]. Plaster molds or specially treated cadaveric bones are the most common models for teaching spinal anatomy. However, plaster molds are not very accurate and are single models, and cadaveric bones are not always easily available and are vulnerable to ethical or legal issues [5]. Zhou et al. [6] randomly assigned 62 orthopedic residents to one of two groups. The control group learned about scoliosis using conventional methods, while the experimental group received additional training using 3D printed models. The experimental group was more successful than the control group in assessing the parietal vertebrae in scoliosis patients, as well as in identifying the structures that needed to be surgically repaired and fused ($P < 0.05$; Tables 1 and 2). The experimental group also scored higher than the control group on interest in learning, learning efficiency, interactions with the teacher ($P < 0.01$), and teamwork ability ($P < 0.05$) measures.

By using 3D printing technology to create realistic models of the spine and the aid of X-ray, CT, MRI, and other images, we can vividly describe clinical spine diseases, investigate disease causes, and discuss and practice the operative phase of surgery. However, 3D printed models have some limitations. For example, they cannot be used in basic education on a wide scale. Abstract theoretical expertise is combined with clinical cases to help train young physicians and students in surgical procedures. 3D printed models are costly and do not lend themselves well to batch manufacturing [7]. The difference between the tactile sensation of 3D printed materials and human anatomical structures can cause errors and adverse effects for practitioners as they perform surgery [8]. Moreover, 3D printed models can only reconstruct bony structures, not the surrounding soft tissues, which is not conducive to teaching precise operative techniques.

2.2. Preoperative Communication and Planning. Spine surgeries are demanding and complicated procedures that necessitate preoperative contact with patients and/or families in order to formulate surgical plans and stabilize the patient. Personalized surgical plans can be explored using 3D printing technology to precisely restore the target spine, and surgical rehearsals can be conducted on models to improve completion, minimize damage, shorten operation time, and formulate plans [9]. Physicians may use 3D printing to communicate the disease and treatment plan to patients who lack theoretical understanding. This helps patients appreciate the treatment, relieves their stress and anxiety, and makes them more cooperative. It also helps patients better understand surgical dangers and prognosis, reducing physician-patient disputes. For a comparative study of pedicle screw placement, Wu et al. [10] divided 62 patients with congenital scoliosis into two groups: a traditional intraoperative fluoroscopy group (C-arm group; 28 patients) and a preoperative expected model group (RP group; 34 patients). The RP group had an overall accuracy rate of 93.5%, whereas the C-arm group had an accuracy rate of 84.7%. The RP group also exhibited higher precision in screw positioning during preoperative preparation, shorter average operating period times, and less bleeding during surgery. Yang et al. [11] conducted a comparison between the groups of physicians who either did or did not use 3D printed spine models for preoperative planning. The group who did use models operated on 50 patients with adolescent idiopathic scoliosis (AIS), and the group who did not use models operated on 76 AIS patients. The former group had significantly lowered operative times, perioperative blood loss, and transfusions. 3D printing technology allows patients and doctors to view accurate and comprehensive bone models before surgery, which aids patient-provider coordination, as well as helping with the creation of highly accomplished, low-injury surgical plans. However, since 3D printed models lack surrounding tissue structures like blood vessels, nerves, and ligaments [9], they are not complete anatomical replications, and there is a risk that the surgical plan could deviate from the actual scenario. 3D printing technology also requires time for modeling: 3D printed models and patient-specific navigation templates can take up to days to prepare, depending on the size of the model and the machine used [9]. Thus, they are not suitable for preoperative planning in patients with critical conditions.

2.3. Intraoperative Assistance. 3D printing technology for skeletal models, navigation prototypes, and personalized aids has proven to be extremely useful in complex spine surgeries. Phan et al. [12] applied a personalized fixation material made using 3D printing technology in a spinal L1-2 fusion surgery, and the patient showed significant improvement in cervical spine condition. However, the functional implications of custom-made 3D printed internal implants are not entirely clear at present, and further study is still needed. Navigation models are 3D printed from imaging data and are used to change the angle, depth, and location of the pedicle screw placement. This has four advantages [13]: the customized design to enhance nail placement accuracy; the navigation model helps streamline surgery and saves time; the procedure reduces radiation exposure during surgery; and there is reduced use of equipment, which reduces costs. Zhu et al. [14] divided 82 patients with lumbar spinal stenosis into two groups: a nail placement group which was supported by 3D printed navigation models (study group; 42 patients) and a traditional nail placement group (control group; 40 patients). The findings showed that study groups' operative time, bleeding, and mean number of fluoroscopic views were all lower than the control groups'. However, pain values (VAS) at three days and one month postoperation, as well as the lumbar spine function values (ODI) at one month postoperation, were higher. Sugawara et al. [15] published the findings of a trial in spine surgery using 3D printing-based pedicle screw guidance templates. With the aid of this reference template, 813 screws were intraoperatively inserted in 103 patients. Postoperative CT imaging confirmed that the screws were completely enclosed inside the pedicle, with no damage to the cortex, blood vessels, or nerves. Resection of spinal cord tumors with unclear boundaries [16] can be performed with the help of a 3D printed tumor model, which will reduce the degree of injury and help surgeons maintain maximum negative margins. After the tumor has been removed, 3D-printed vertebrae can be used to replace diseased vertebrae. 3D printing technology enhances surgical procedure safety, decreases the risk of surgical errors, improves surgical completion, and expands the range of options available during surgery. However, as previously mentioned, customized 3D models are time-consuming to build (taking anywhere from two hours to two days to complete), and personalized templates necessitate separate software designs [4], which is incompatible with the needs of patients with critical illnesses. Furthermore, according to one survey [17], few 3D navigation models have actually been used intraoperatively. Larger sample sizes, clinical follow-up,

Table 1: Comparison of the correct rate of scoliosis tests.

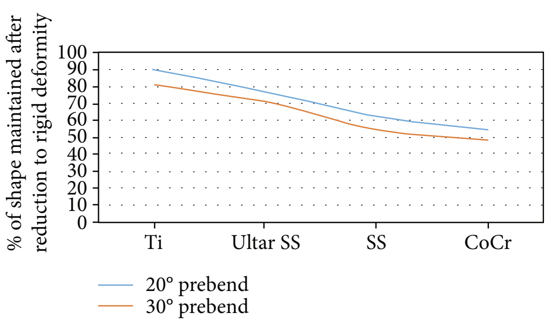
Project	Experimental group (%)	Control group (%)	χ^2	P
The apical vertebrae of scoliosis	83.8	58.1	5.01	0.025
The planned surgery of segment	77.4	51.6	4.51	0.034

Table 2: Comparison of questionnaire assessment results.

Project	Experimental group ($\bar{\chi}^{\pm s}$)	Control group ($\bar{\chi}^{\pm s}$)	t	P
Learning interest	(4.26 ± 0.86)	(3.26 ± 1.27)	3.28	<0.01
Learning efficiency	(3.81 ± 0.83)	(3.0 ± 0.73)	4.29	<0.01
Proactive interaction	(4.1 ± 0.79)	(3.42 ± 0.77)	3.50	<0.01
Teamwork ability	(3.1 ± 1.01)	(2.65 ± 0.61)	2.19	<0.05

Table 3: Mechanical properties of three major spinal implants in AIS surgery.

Biomaterial	Young's modulus/elastic modulus (Gpa)	Yield strength (MPa)	Fatigue strengh (MPa)
Stainless steel	190	792	241-820
CoCr alloys	200-300	300-2000	207-950
Titanium alloys	110-116	485-1034	300-389



Curvature	Ti	Ultar SS	SS	CoCr
20° prebend	90.0	77.0	62.5	54.4
30° prebend	80.7	71.0	54.6	48.1

Figure 1: Plastic deformation of rods at 20° and 30° curvature for four materials.

and testing of the basic advantages and drawbacks of 3D templates are still needed.

2.4. Postoperative Rehabilitation. 3D printing can be used both preoperatively and intraoperatively. It can improve surgical completion accuracy, reduce trauma to patients during surgery, and allow for better prognosis and recovery. Spetzger and Wu each used individualized 3D printed intervertebral fusion devices in cervical spine surgery. Both studies found that the 3D printed models matched the patient's anatomy well and had good spinal stability, reducing the risk of postoperative dislocation and promoting postoperative rehabilitation efficiency [18]. After spine surgery, however, patients also require a period of functional exercise and rehabilitation. At this stage, 3D printing technology can be used to create customized tailored rehabilitation supports that are more closely suited to individualized spine curvatures, positions, and sizes in order to meet the various pathological needs of patients and perform more efficient functional recovery. 3D printed supports made of rich materials also outperform conventional plaster or plastic rehabilitation supports in terms of weight, comfort, and breathability [19]. Furthermore, 3D printed braces can be linked to monitoring systems for joint biomechanical analysis [9], postoperative recovery monitoring, functional exercise assistance, and adjustment of rehabilitation plans. However, due to price, material, and technology limitations, customized rehabilitation braces are only appropriate for a limited number of patients or those with complicated conditions and are not widely used in clinical settings.

3. 3D Printing Technology and Osteoporosis

Osteoporosis (OP) is a disorder in which bone mineral density, bone strength, and bone durability are all diminished, and a patients' BMD T-score (a screening method for osteoporosis) is less than 2.5 standard deviations [20]. Osteoporosis is often characterized by reduced bone tissue content, irregular bone structure, and increased bone fragility, increasing the risk of secondary fractures [21].

Geriatric osteoporosis is most common in people over the age of 70, and it is caused by tissue cellular hypofunction, which inhibits calcium absorption. Adolescents are particularly susceptible to idiopathic osteoporosis, which has no clear cause. Postmenopausal osteoporosis occurs primarily in women 5-10 years after menopause as a result of a decrease in calcitonin caused by a decrease in estrogen, which indirectly inhibits osteoclasts functioning, resulting in bone resorption, rather than bone formation [22, 23]. Patients' fracture risks are increased by changes in bone

Table 4: Comparison of the Vickers hardness and compressive properties between Ti–TiB, CP-Ti, and Ti–6Al–4 V composites.

Reference	Material type	Condition	Vickers hardness (HV)	Ultimate comprehensive strength (MPa)	Yield strength (MPa)	Maximum strain (%)
[27, 28]	CP-Ti	Casting/ECAP	210	900	700	35
[29, 30]	Ti-6AI-4 V	Superplastic forming/annealed	346	1300	1000	10
[31]	Ti-TiB	SLM	402	1421	1103	17.8

microarchitecture, progressive loss of bone strength, and progressive loss of bone mass [24]. Maquer et al. [25] showed that, due to differences in elastic properties, it is difficult to make similar bone trabeculae commercially. Barak et al. [26] used 3D printing to replicate the same structural bone trabeculae and developed standardized trabecular structural bone models (which employed different thicknesses of bone trabeculae based on differing segmentation thresholds) for use in postmenopausal osteoporosis care. Severe complications—including prosthetic interface displacement, loosening, and periprosthetic fractures—are amongst the biggest clinical challenges in osteoporotic arthroplasty [27, 28]. Furthermore, while titanium is the most widely used material for orthopedic implants due to its high mechanical strength and corrosion resistance, it is very stiff, which can result in stress shielding-induced osteolysis [29, 30]. 3D printed porous titanium (pTi) scaffolds can be significantly stiffened and printed to meet desired shapes and surface areas [31–33]. However, pTI implants can fail due to inadequate bone integration because they have very smooth surfaces and poor osteogenesis cellular adhesion [34, 35]. Dobson et al. [36] used micro-CT scans of 4 mm^3 human bones using micro-stereolithography to build 3D printed models which could validate finite element (FE) predictions of osteophyte structures. The 3D printed models were tested with compression, and their stiffness values correlated strongly with the values the FE analysis had predicted. 3D printed models are an important technique to complement the use of FE models for assessing the mechanical properties of complex osteophytic structures. 3D printing technology can accurately simulate bone trabecular structures, which gives 3D printing an advantage over other conditions such as material aging, implant rejection, and fossil bone trabecular samples. 3D printing can also help personalize osteoporosis treatment and predict fracture risk [26]. Further, it can assist in curing osteoporosis by creating bone trabeculae which have incredible structural properties. However, the materials used to create these trabeculae still need further testing and refinement.

4. 3D Printing Metal Materials

Metals, ceramics, and polymers are among the numerous 3D printing materials available today. Internal implants are often used in spinal surgery, and 3D-printed internal implants are primarily made of metal and biomaterials. Stainless steel, cobalt-chromium alloy, titanium, and other metals are commonly used in clinics. Stainless steel has a lower carbon content, as well as improved mechanical and biocompatibility properties. However, it is also fragile and susceptible to low-stress values; so, it is more likely to fail under physiological loading conditions [37]. The cobalt-chromium alloy is a high-temperature alloy composed of Co and Cr with high corrosion resistance, fatigue strength, and yield strength. It has more mature applications in the medical field. However, over time, it can corrode and release harmful ions [38]. Ohrt-Nissen et al. examined stainless steel, cobalt-chromium alloy, and titanium materials that were examined in adolescent idiopathic scoliosis surgery [39]. As shown in Table 3, titanium has a high yield strength (485-1034 MPa), a low Young's modulus (110-116 GPa), and low fatigue strength (300-389 MPa). Although cobalt-chromium alloy has the highest yield strength and the lowest fatigue strength, the value span is excessive, which means there is a high possibility of instability. Stainless steel performed substantially worse than the other two types in three places. Serhan et al. conducted an experiment [40] in which 40 5.5 mm spinal rods were made from four materials: stainless steel, titanium, cobalt-chromium alloy, and ultra-high strength stainless steel (UHSS), divided equally into four groups, and then cut at 20° ($n = 5$) and 30° ($n = 5$) angles. The apical pedicle screw was subjected to a rod approximation force, and deformation of the four materials was compared. As shown in Figure 1, after being stressed under the condition of rod bending at 20°, Ti, UHSS, stainless steel, and cobalt-chromium alloy preserved 90%, 77%, 62.5%, and 54.4% of their original shapes, respectively, and preserved 80.7%, 71%, 54.6%, and 48.1% of their original shapes, respectively, after being stressed under the premise of rod bending at 30°. Thus, titanium best preserved its original morphology and had the highest overall ranking of all of the materials.

Titanium, the most widely used of these materials, has low density, high strength, low Young's modulus, high corrosion resistance, and high biocompatibility [41–43]. The most popular titanium-based materials used in traditional orthopedic endosseous implants are commercially pure titanium (CP-Ti) and Ti-6Al-4 V. However, the relatively large density, stiffness, and modulus of elasticity variations of titanium-based materials compared to human bone tissue may affect their biomedical applications [44, 45]. Therefore, adding ceramic, plastic, or other biologically inert materials to titanium-based materials can increase the yield strength (which is the stress at which permanent deformation occurs) and ultimate compressive strength. Titanium alloy, as the primary metal material used in clinical applications, has high reconstructed spine structure stability and high yield strength, but low stiffness. Furthermore, titanium alloy-based microporous metal implants have higher safety and efficacy scores. Zhang et al. [44] compared the Vickers hardness, yield strength, compressive ultimate strength, and maximum strain of composites produced by selective laser melting (SLM) to those of CP-Ti and Ti-6Al-4 V produced by other techniques. Table 4 [46–50] shows that the Vickers hardness of Ti-TiB (402 HV) was greater than that of CP-Ti (210 HV) and Ti-6Al-4 V (346 HV); the yield strength of Ti-TiB (1103 MPa) was greater than that of CP-Ti (700 MPa) and Ti-6Al-4 V (1000 MPa), and that the compressive strength and maximum strain values of Ti-TiB are greater than those of typical CP-Ti and Ti-6Al-4 V. While differences in fabrication techniques can play a role, clinical trials show that titanium alloys are much more effective than pure titanium. Additionally, although titanium has been used in spine surgery for a long time with good results, findings are often focused on a small, individualized number of cases. It is unknown whether the mechanical strength and properties of titanium alloys would be compatible with current data if 3D printing technology could achieve mass production, and ongoing evaluation studies are needed [13]. There are fewer types of materials that lend themselves well to 3D printing, because they must simultaneously meet the complex requirements of protection, compatibility, and degradability [38]. Additionally, 3D printing materials must undergo clinical trials before they can be used in manufacturing. Materials research that involves modifying the structural shape of materials or research that involves mixing metals with biological cellular materials, could lead to more application possibilities.

5. Outlook

The spine is one of the body's most significant skeletal structures, and spine surgery is a meticulous operation that involves disc structures, adjacent tissues, physiological curvature, and gravity effects. 3D printing technology has only been in use for a few decades, but it has already led to breakthroughs in orthopedic spine surgery, solving issues that were previously unsalvageable and providing further hope for medical progress. 3D printing is still an emerging technology; however, relevant regulations have not yet been perfected, clinical applications are limited due to high costs, and it has not yet been applied widely outside of a few complex cases. Nevertheless, with recent emphasis on innovative medical technologies, the utility of raw materials for 3D printing has increased, the costs are decreasing, and efficacy is improving. Different 3D printing structures and materials are required when it is applied to different types or degrees of osteoporosis, but the therapeutic effects for this condition still need further research. The development of 3D printing technology in medicine also involves industrial production, software design, physical and chemical research, and many other fields. For example, raw material research may increase material potential by modifying its structures, altering manufacturing techniques, changing joining methods, and expanding the variety of materials available. In addition to metal materials, which are the most commonly used, bioprinting materials have started to receive attention in recent years. Active biomaterials with nutrients are more suitable for in vivo placement. However, further research is needed to mitigate rejection of nonautogenous cells. Other 3D printing research is related to the manufacturing of controlled-release drugs and their application to the rehabilitation phase of spinal surgery. Controlled-release drugs are introduced into internal implants using 3D printing, and the drug effect is quantitatively and directly applied to the spinal site to optimize postoperative rehabilitation. Future 3D printing research could also network platforms using artificial intelligence, collect big data, and exchange and summarize the success of research experiments, thus laying the groundwork for the standardization and popularization of 3D printing technology. Much of research on 3D printing is still in its early stages, but it is certain to have broader medical applications and benefits in the future.

Data Availability

There is no laboratory data in this study, and the review process and references are corrected and put in the Data Center of Heilongjiang University of Chinese Medicine for 8 years.

Conflicts of Interest

The authors have no conflicts of interest to declare regarding the publication and content of this manuscript.

Authors' Contributions

Bing Wang, Chuwen Feng, and Jianyu Pan contributed equally to this work. Yang Li and Tiansong Yang made critical revisions to the manuscript. All authors read and approved the final manuscript.

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Retraction

Retracted: Application Experience and Patient Feedback Analysis of 3D Printed AFO with Different Materials: A Random Crossover Study

BioMed Research International

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This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope

(2) Discrepancies in the description of the research reported

(3) Discrepancies between the availability of data and the research described

(4) Inappropriate citations

(5) Incoherent, meaningless and/or irrelevant content included in the article

(6) Manipulated or compromised peer review

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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[1] X. Meng, M. Ren, Y. Zhuang, Y. Qu, L. Jiang, and Z. Li, "Application Experience and Patient Feedback Analysis of 3D Printed AFO with Different Materials: A Random Crossover Study," *BioMed Research International*, vol. 2021, Article ID 8493505, 6 pages, 2021.

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Research Article

Application Experience and Patient Feedback Analysis of 3D Printed AFO with Different Materials: A Random Crossover Study

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Purpose. This study is aimed at analyzing the application experience and feedback of the patients with poststroke ankle dorsiflexion disorders for 3D printed AFO with three different materials. *Methods*. 15 patients were randomly divided into three groups; 3D printed AFO with 3 different materials (PA2200, Somos NeXt, and PA12) was used to each group, according to the crossover study design, in order to ask the three groups of patients to use three different materials of 3D printed AFO. Assessment was taken by the end of each test round. Through statistical processing, the patient feedback data of the three groups of materials of 3D printed AFO were obtained. *Results*. In the material comfort assessment of the AFO, Somos NeXt was compared with PA2200, and the p value was <0.05; in the item of surface smoothness of the AFO, Somos NeXt was compared with PA2200, and the p value was <0.01; at the same time, PA12 was compared with PA2200, and the p value was <0.05. *Conclusion*. The 3 different materials of 3D printing AFO bring different experience, and we also have sufficient reason to believe that there will be differences in the auxiliary effect of this on patients, which leads the patient's selection too. The material Somos NeXt is much popular and has certain clinical advantages.

1. Introduction

Three-dimensional printing (3D) is one of additive manufacturing technologies, which appeared in the 1980s. It establishes the 3D data of the target model by means of CT, MRI, CAD, or 3D scanning, processes it into a 3D digital model file by reverse engineering modeling software, then transmits it to a suitable printer, and finally selects suitable materials to print the target model layer by layer. Because 3D printing technology has the advantages of personalized customization, the ability to manufacture complex and fine structures, high material utilization, and short manufacturing cycle has been widely used in the medical field, such as the application of ankle foot orthosis (AFO) in rehabilitation medicine. Poststroke patients are often accompanied by paralysis of the lower limbs, foot drop, and varus [1]. For these patients with ankle dorsiflexion disorders, the configuration of AFO can effectively improve hemiplegic gait and improve walking function. However, there are some defects in traditional orthoses, such as the inability to achieve personalized design for plaster or splint fixation, and may cause serious skin infections, limb stiffness, pressure sores, and other complications; low-temperature thermoplastic plates need to be adjusted repeatedly when manufacturing orthoses, which has the risk of scalding patients; the manufacturing process of high-temperature plastic orthosis is cumbersome, the efficiency is low, and the appearance is unsightly [2]. 3D printing technology completes the construction of the whole entity through layered processing and superposition molding, which can achieve design freedom and can be optimized according to personal biomechanical requirements to provide patients with better orthopedic functions and better appearance design [3]. 3D printing AFO may improve patient satisfaction, wearing compliance, and the quality of life of patients [4].

The commonly used materials for 3D printers include plastics, metals, resins, nylon, hydrogels, ceramics, and composite. Currently, the most commonly used technologies include stereo lithography appearance (SLA), fused deposition modeling (FDM), selective laser sintering/melting

(SLS/SLM), laminated object manufacturing (LOM), and three-dimensional jet printing (3DP) [5]. This study is aimed at comparing the actual printing effects of the three commonly used printing materials for orthotics and exploring their application experience and feedback in patients with poststroke ankle dorsiflexion disorders [6].

Crossover design is normally used as another important study design for clinic trial when the study needs the patients to use two or more interventions, allowing the patient to compare themselves. Its advantage is that the same patient receives two or more interventions successively and obtains two or more results; this type of design can reduce the number of samples, and it has better ethics and economics [7]. However, due to the washout period and sequential clinical intervention steps, crossover study design also has disadvantages: (a) it is only suitable for symptomatic treatment of chronic recurrent diseases; (b) observation time is prolonged, and patients are likely to be lost to follow up, withdraw, and decline compliance; (c) research on diseases that are not suitable for acute onset and short course of disease. It is precisely because of the characteristics of crossover design that this type of design is suitable for this study [8].

2. Clinical Data

2.1. Research Object and Grouping. Patients with poststroke ankle dorsiflexion disorders in the Rehabilitation Department of the Shanghai Pudong New Area People's Hospital from July 1, 2020, to December 31, 2020. Finally, according to the inclusion and exclusion criteria, a total of 15 subjects were determined and randomly divided into three groups: group A, group B, and group C.

2.2. Diagnostic Criteria. The diagnostic criteria of stroke were formulated with reference to the Chinese Guidelines for Diagnosis of various cerebrovascular diseases.

2.3. Inclusion Criteria. The inclusion criteria of this study were as follows: (1) a minimum of 3-month poststroke with hemiparesis; (2) an ability to walk safely with the use of an AFO; (3) participation is voluntary, and informed consent has been signed.

2.4. Exclusion Criteria. The exclusion criteria of this study were as follows: (1) patients with severe pain or musculoskeletal issues and (2) patients with cognitive issues [9].

3. Intervention and Crossover Design

3.1. Data Acquisition and Preparation before Brace 3D Printing. Artec and 3D scanner (EinScan-Pro, Shining 3D scanner company) were used to scan the legs, ankles, and feet of paralyzed limbs. Sitting or lying position was required. After scanning, the initial AFO 3D model image can be obtained. Then, the software Geomagic Studio was used to modify, and surface treatment of the AFO model (STL file type) designed a reasonable AFO shape; the key processing procedures include the following: according to the design requirements, deleted the extra patch; used tools of "Remove Feature," "Fill Single Hole," "Fill All," and other tools to repair the broken hole; smoothed boundary lines and set thickness value.

3.2. Brace 3D Printing with Different Materials. After the design was completed, the AFO model was output in STL file format, and the required AFO was printed by a 3D printer. This study involved 3 different materials: PA2200 [10], Somos NeXt [11], and PA12 [12]. The material PA2200 is characterized by high strength, light weight, and toughness, and the printing method is SLS [10]. The material Somos NeXt is white, with high strength and toughness and good precision and appearance, and the printing method is SLA [11]. The material PA12 has extremely low moisture absorption, excellent mechanical strength, and good wear resistance and corrosion resistance, and the printing method is MJF [12].

3.3. Crossover Design. Random grouping was carried out according to the patient's medical record number. The 15 patients' medical record numbers were arranged from small to large, so that every five persons were divided into a group. Three groups were set, group A, group B, and group C. Each group had 5 patients. The patients were all informed and signed an informed consent, respectively [7].

During the experiment, the patients would not know the specific plan of the material used in the brace, and they only be notified that a new brace would be replaced after the wash-out period, in order to set up blind barriers [7].

From the beginning, we set group A to use 3D printing AFO with material 1, group B to use 3D printing AFO with material 2, and group C to use 3D printing AFO with material 3. After wearing for one week, all the patients have 2 days to take a pause for rest and also for the wash-out period. Next, group B took material 1, and group C took material 2, while group A took material 3, wearing one week and two-day wash-out period. In the last round, group C took material 1, group A took material 2, and group B took material 3, wearing one week. The assessment points would be on the last day of each round [7]. See Figure 1.

4. Evaluation

(1) *Evaluation Items*. The study sets 7 assessment items as shown below:

(a) Material comfort assessment of the AFO

(b) Weight feeling of the AFO

(c) Surface smoothness of the AFO

(d) Difficulty in wearing

(e) Convenience of cleaning

(f) Skin lesion

(g) The occurrence of adverse events

We set up score sheets for each assessment item above, and the NRS system concept was used. The 100 was set as prefect, while the 0 was set as the worst. See Figure 2.

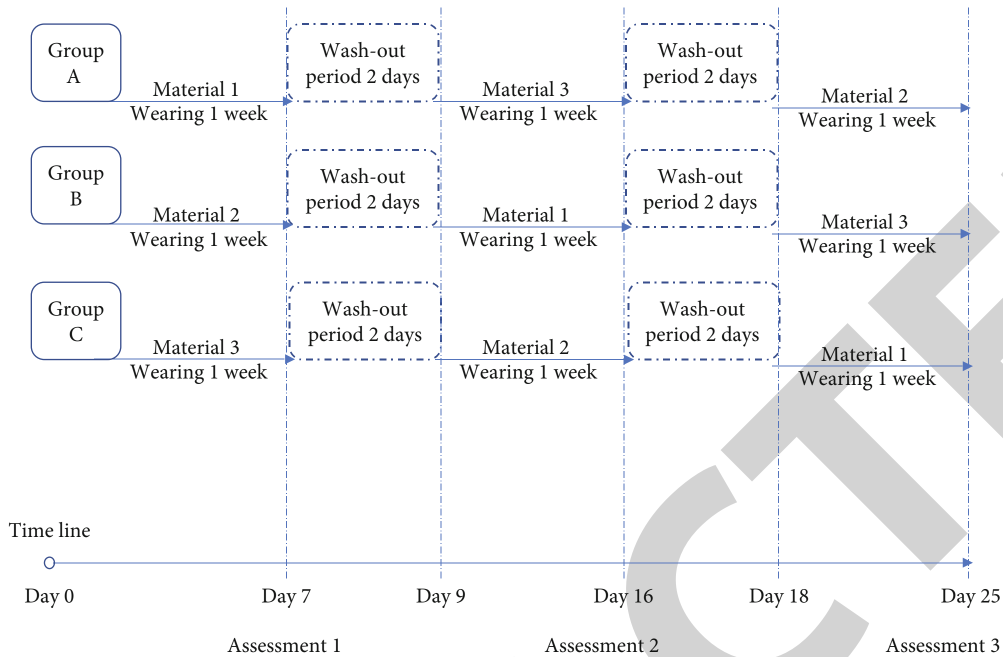

Figure 1: Crossover study design.

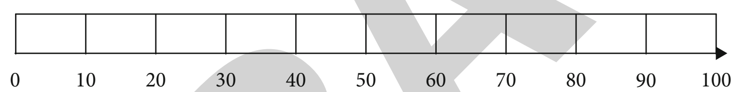

Figure 2: NRS system concept.

(2) *Evaluation Points*. The assessment points would be on the last day of each wearing round. It meant the day 7, day 16, and day 25.

(3) The evaluation was made by an independent researcher; she collected the data with self-sufficient and contacted with the study participants

5. Statistical Methods

Data of material comfort, weight, surface smoothness, difficulty in wearing, convenience of cleaning, and skin lesion were collected in on MS Excel file, and material classification as a parameter was used to integrate three parts of data. With the IBM SPSS 22.0 Statistics Software, one-way ANOVA LSD and T3 were used to detect the difference among the three parts, in order to make decision whether the three parts of data were able to merge. After that, three types of different materials of 3D printing AFO feedback data were received. Based on these feedback data of three materials, each material data had 7 parameters, which were also the 7 comparison items mentioned above. One-way ANOVA was taken again to make a statistical analysis.

6. Results

(1) The possibility of data merge

Taking the material as the parameter, groups A, B, and C provided three parts of the data, and the comparison results showed that there was no significant difference among the three parts. It indicated that the order of wearing had no correlation with the brace data of different materials.

(2) After data merge, three types of different materials of 3D printing AFO feedback data were received. The comparison results are indicated in the material comfort assessment of the AFO; Somos NeXt was compared with PA2200, and the p value <0.05 means there is a significant difference; in the item of surface smoothness of the AFO, Somos NeXt was compared with PA2200, and the p value <0.01 means there is a great significant difference, and at the same time, PA12 was compared with PA2200, and the p value <0.05 means a significant difference. See Figures 3 and 4 and Table 1

7. Discussion

AFO can effectively improve the kinematics and dynamics parameters of the ankle and knee joints and is mainly used for walking and correcting deformities of drooping feet and clubfoot. The preparation of traditional AFO relies on handwork, which requires a high level of skill and a lot of meticulous work by the maker; however, with 3D printing technology, we only need to enter the design parameters once, which can be used for life, which greatly facilitates the replacement and adjustment of subsequent orthotics. AFO

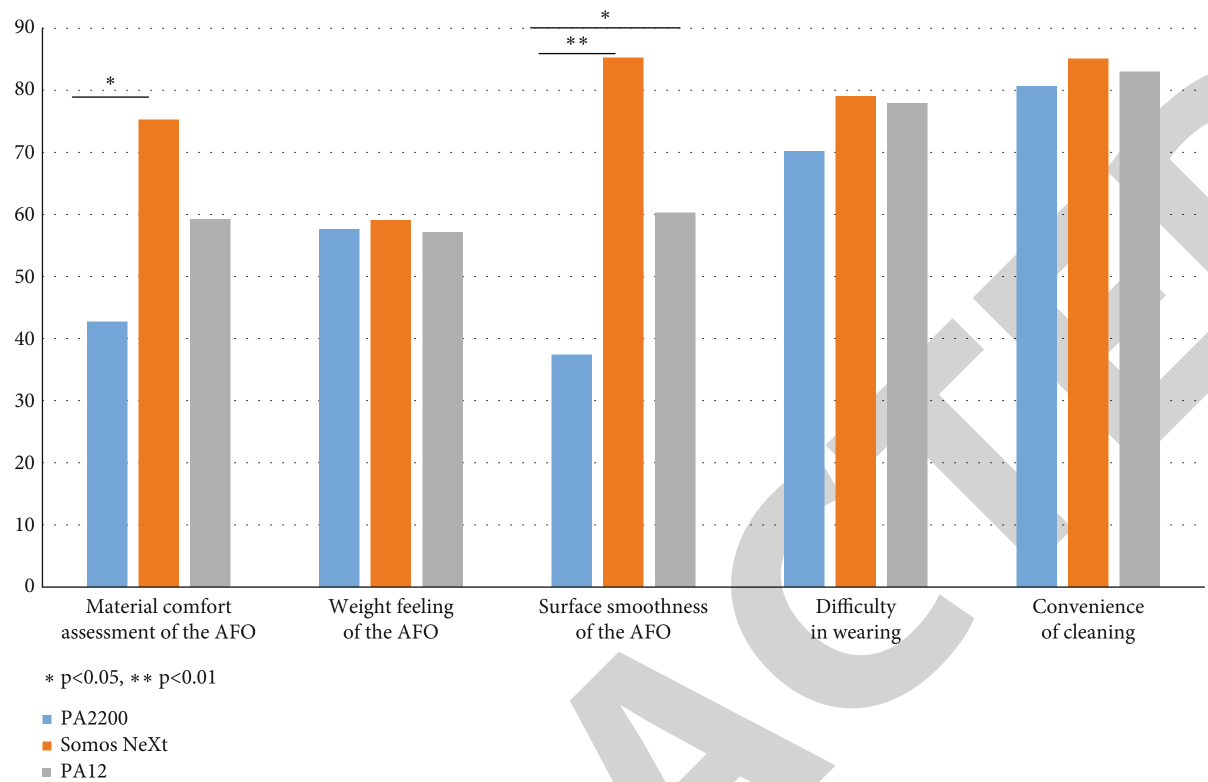

Figure 3: Comparison histogram among different materials.

Figure 4: Comparison radar map among different materials.

Table 1: Three different material comparison data.

	PA2200 mean (SD)	Somos NeXt mean (SD)	PA12 mean (SD)
Material comfort assessment of the AFO	42.73 (30.52)	75.31 (26.88)*	59.22 (36.01)
Weight feeling of the AFO	57.65 (10.63)	59.06 (16.91)	57.13 (20.82)
Surface smoothness of the AFO	37.40 (9.05)	85.26 (17.80)**	60.27 (28.11)*
Difficulty in wearing	70.18 (19.66)	79.06 (27.05)	77.91 (30.01)
Convenience of cleaning	80.69 (6.02)	85.07 (10.22)	83.00 (11.74)
Skin lesion	None	None	None
Adverse events	None	None	None

*Compared with PA2200, $p < 0.05$; **compared with PA2200, $p < 0.01$.

printed by 3D has high design flexibility and strong personalized customization ability, which can put on "beautiful shoes" for patients and improve their self-confidence. Cha et al. [13] designed a 3D printed AFO for a 68-year-old female foot drop patient and compared the use effect with the traditional AFO, and the results show that 3D printed AFO can make the patient's left and right foot posture more symmetrical when walking, that is, walking is more natural and stable; moreover, 3D printed AFO has a better effect on preventing foot drop and is easier to wear than traditional AFO.

The printing method of 3D printing and the material properties of the printing materials are important factors that affect the printing effect. In recent years, some studies have adopted different printing materials, carried out some mechanical tests including accuracy and bending strength, and conducted a few clinical studies. Mavroidis et al. [6] established the AFO model by scanning ankle and foot with 3D scanner and printed AFOs of two different materials. One AFO which was printed of Accura 40 resin was hard, and the other which was printed of DSM Somos 9120 was soft. Both of the AFOs have high precision and the same clinical effects compared with traditional AFO products [3].

Crossover design's advantage application to that the same patient can receive different interventions at different stages, and the washout period between the two interventions effectively blocks the delayed effects of the interventions. In this study, the AFO brace function is the same, but made from 3 different materials. The brace itself does not have a long-term delayed effect on patients; therefore, this study does not require a long washout period [2, 8]. The same patient tries 3 different materials of AFO braces, and each patient's comparative data comes from herself/himself, which objectively guarantees the consistency of subjective feelings, which plays a vital role in the stability and accuracy of experimental data. Randomly dividing into three groups, to a certain extent, avoided the impact of the intervention sequence of the three different materials of 3D printed braces on the subjective feelings of the patients and increased the comparability of the data.

It can be learned from this study that the actual printing effects of the three materials are different. In this experiment, we used 3 printing methods to print 3 different materials; Somos NeXt used SLA printing, PA2200 used SLS printing, and PA12 used MJF printing. All AFOs have high accuracy, which matches the ankle and foot of patients. This result is consistent with the expectations, reflecting the advantages of 3D printing technology and meeting the technical parameters of the three materials. From the view of material comfort and surface smoothness, PA2200 gets the lowest score, while the Somos NeXt gets the highest; this is certainly related to the printing method, but it also reveals the disadvantages of this material. Participants' feedback also shows Somos NeXt is the easiest for wearing and cleaning. No skin lesion and adverse events happened [10–12].

In summary, the 3 different materials of 3D printing AFO bring different experience, and we also have sufficient reason to believe that there will be differences in the auxiliary effect of this on patients, which leads the patient's selection too. The material Somos NeXt is much popular and has certain clinical advantages.

Data Availability

The study data used to support the findings are kept by the project team data center of Pudong New Area People's Hospital, and requests for data will be considered by the data center.

Ethical Approval

This study was approved by the Medical Ethics Committee in Pudong New Area People's Hospital, No.: PDWJXK-1713.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Xianzhong Meng was the leader of the project in this study; Zhenjing Li is the main implementer and project designer; Min Ren, Yan Zhuang, Yu Qu, and Linling Jiang were responsible for communicating directly with patients and collecting data.

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Review Article

Development and Application of Medicine-Engineering Integration in the Rehabilitation of Traumatic Brain Injury

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The rapid progress of the combination of medicine and engineering provides better chances for the clinical treatment and healthcare engineering. Traumatic brain injury (TBI) and its related symptoms have become a major global health problem. At present, these techniques has been widely used in the rehabilitation of TBI. In this review article, we summarizes the progress of the combination of medicine and industry in the rehabilitation of traumatic brain injury in recent years, mainly from the following aspects: artificial intelligence (AI), brain-computer interfaces (BCI), noninvasive brain stimulation (NIBS), and wearable-assisted devices. We believe the summary of this article can improve insight into the combination of medicine and industry in the rehabilitation of traumatic brain injury.

1. Introduction

With the development of the society, traumatic brain injury (TBI) is gaining more attention because of its higher rates of morbidity and mortality. It is defined as a traumatic structural or physiological disruption of brain function, mainly caused by an external physical force. Traumatic brain injury (TBI) is the mainly common cause of death and disability in those aged under 40 years in the UK [1]. TBI still plague millions of peoples around the world every year [2]. Though the efforts for exploring therapeutic strategies for the rehabilitation of TBI have been taken over the past few decades, there is still a lack of effective treatment for it, and the treatment of TBI is far from satisfactory. Meanwhile, the combination of medicine and engineering brings new rehabilitation methods to TBI patients. The combination of medicine and engineering is a newly developed interdisciplinary subject in recent years, which is the product of the integration and innovation of medical science and engineering science, and it brings new idea to this significant public health issue. In this review article, we outline recent breakthroughs in the combination of medicine and engineering and their applications in the rehabilitation of TBI. We believe the summary of this article can improve insight into the usage of the combination of medicine and engineering in TBI's rehabilitation. As shown in Figure 1, we mainly describe advances including artificial intelligence (AI), brain-computer interfaces, and noninvasive brain stimulation (NIBS) et al.

2. Artificial Intelligence (AI)

Artificial intelligence is a broad interdisciplinary field, which is composed of logic, cognitive psychology, decision theory, neuroscience, linguistics, computer engineering, and so on [3]. As time goes by, artificial intelligence is gradually changing the clinical practice of medicine. With the continuous

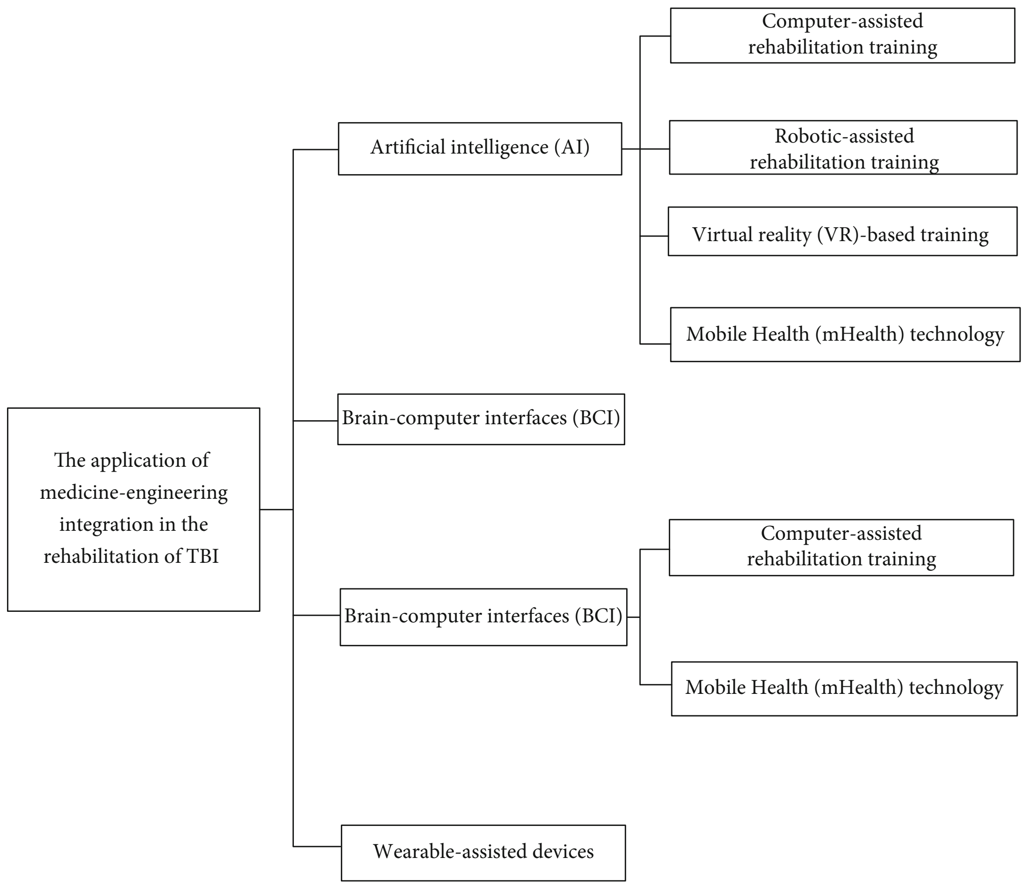

Figure 1: The application of Medicine-Engineering integration in the rehabilitation of TBI.

development of digital data acquisition, machine learning, and computing foundation, the application of artificial intelligence is expanding to the field previously considered as human experts [4]. The fields of traumatic brain injury (TBI) and artificial intelligence (AI) have been studied for a long time. In recent years, artificial intelligence (AI) is applied in the rehabilitation of traumatic brain injury (TBI) widely. The application of AI in TBI's rehabilitation mainly including computer-assisted rehabilitation training, robotic-assisted rehabilitation training, virtual reality (VR), and smart mobile technology.

2.1. Computer-Assisted Rehabilitation Training. Cognitive dysfunction is one of the main consequences of traumatic brain injury (TBI). Cognitive impairment leads to a serious decline in the quality of life after TBI and is involved in the impact of depressive symptoms on emotional role functioning [5]. By far, computer-assisted rehabilitation training has been widespread application in the cognitive rehabilitation in people with traumatic brain injury (TBI).

A study of 35 patients with traumatic or vascular brain injury found that compared with conventional treatment, cognitive training can effectively improve the rehabilitation effect after TBI, which brings new hope for TBI patients [6]. In this study, they detail an introduction to how computer-assisted cognitive rehabilitation (CACR) uses multimedia and informatics resources directly to utilize specific hardware systems and software to activate the expression of impaired neurocognitive function through specific programs. In 2013, Cruz et al. developed a new Web-based rehabilitation tool called "COGWEB" that intensive cognitive training is provided at home at an affordable cost under clinical prescription and supervision, compared with previous traditional cognitive rehabilitation technique. The COGWEB system motivated the treatment positive of patients with traumatic brain injury [7]. Dou et al. conducted a clinical study to evaluate the efficacy of computerized error-free learning memory rehabilitation program for Chinese patients with traumatic brain injury (TBI) in 2006. The result indicated that computer-assisted memory rehabilitation (CAMG) improved the memories of patients with TBI [8]. Another study examined the effectiveness of computer-assisted cognitive rehabilitation (CACR) in patients with traumatic brain injury (TBI), the result found that CACR significantly improved the cognition of TBI patients, but the extent and nature of these gains remains to be further studied [9]. In the above, we can know that computer-based interventions seem to hold great promise in improving working memory in people with acquired traumatic brain injury, but it is more commonly used for cognitive rehabilitation after traumatic brain injury and the durability of its efficacy remains to be studied. Meanwhile, a systematic review and meta-analysis found that computer-assisted rehabilitation training might be a benefit to improve visual and verbal

Table 1: The advantages and disadvantages of computer-assisted rehabilitation training.

Computer-assisted rehabilitation training	
Advantages	(1) Overall function increase significantly [6]. (2) The simplicity of its use and comfort [7].
Disadvantages	(1) Lack of studies to determine the possible side effects of these interventions [7].

working memory for TBI patients, but other domains such as attention, processing speed, and executive functions were not benefited by the interventions [10]. We can learn that the application of computer-assisted cognitive rehabilitation (CACR) in TBI rehabilitation remains to be further explored. The advantages and disadvantages of computer-assisted rehabilitation training are summarized in Table 1.

2.2. Robotic-Assisted Rehabilitation Training. In the past decades, rehabilitation robots have been rapid and vast developments. As a relatively young and rapidly developing field, rehabilitation robots are increasingly infiltrating into the clinical environment [11]. An increasing number of patients are suffering from limb motor dysfunction, which may be caused by stroke-related nerve damage, traumatic brain injury, or multiple sclerosis [12]. The robotic-assisted rehabilitation therapy can deliver high-quality training to enhance the recovery process and promote the recovery of limb function.

One study presented the application of novel self-feeding robots in TBI rehabilitation, and the self-feeding robots improved the activities of daily living of patients with TBI [13]. In another study [14], Zeng et al. recruited 2 patients with TBI to evaluate the application of collaborative wheelchair assistant system (CWAS) in cerebral palsy and traumatic brain injury users. The results showed that CWAS improved the patients' motor function. Meanwhile, robotic gait training is applied in gait impairment after TBI widely. In 2016, Stam et al. [15] reported a case study that uses robotic gait assistive technology is beneficial for the rehabilitation of participants with TBI. Another study also confirmed that robotic-assisted locomotor training can improve the locomotor performance of patients with TBI [16]. In a study of 16 participants with TBI receiving 18 robotic gait training duration six weeks, the result of this study demonstrated that robotic-assisted treadmill training (RATT) improves step length greater than manually assisted treadmill training (MATT) [17]. Ozgur et al. designed Configurable Arm Rehabilitation Games for patients with chronic upper limb impairment after TBI. The gamified rehabilitation platform using tangible robots can well promote the rehabilitation of limb function [18]. In addition, Brewer et al. designed a model called visual feedback distortion for the rehabilitation of patients with TBI [19]. Two patients were enrolled in a six-week rehabilitation program. In this case, patients who are physically capable of advancing in rehabilitation did not prevent them because they had reached habitual or self-imposed limits, and each patient followed the level of visual feedback distortion higher than her performance predicted in the initial evaluation.

Table 2: The advantages and disadvantages of robotic-assisted rehabilitation training.

Robotic-assisted rehabilitation training	
Advantages	(1) The increase in mobility is beneficial to learning, communication, motivation, and social interaction [14]. (2) Better steerability [14]. (3) Higher intensity gait therapy [16].
Disadvantages	(1) Lack of personalized robot-assisted training (e.g., speed parameter) [17].

In the above, we can learn that robotic-assisted rehabilitation training pays more attention to the limb motor dysfunction after TBI; in my opinion, we should focus on the robot research of hand fine motion rehabilitation in the future. The advantages and disadvantages of robotic-assisted rehabilitation training are summarized in Table 2.

2.3. Virtual Reality- (VR-) Based Training. Virtual reality (VR) is a new and developing technology, which combines the characteristics of VR technology such as autonomy, interactivity, and existence with rehabilitation training. VR is described as "an advanced human-computer interaction mode that allows users to interact in a natural way with a computer-based environment for training and full immersion." [20]. VR is now offering more new treatment measures for patients with TBI.

A study of 33 TBI patients examined the usability of a virtual reality driving simulator [21]. All patients were asked to perform a VR driver rehabilitation (VR-DR) system and completed the related User Feedback Questionnaire. The result found that the VR-DR system could be well applied to the rehabilitation training of TBI patients. Another study tested the availability and efficacy of a newly developed virtual reality- (VR-) based community living skills training program for people with TBI, and the result suggested the produced positive changes in TBI subjects [22]. The study of 18 patients with severe TBI found that through two consecutive days of 3D-cancellation in an interactive virtual environment, VR and robotics technology improved the attention impairment in patients with TBI [23]. Similarly, Bisson's study also shown that rehabilitation training in an interactive visuo-haptic environment may be beneficial to the early recovery of attention in patients with TBI [24]. Additionally, virtual reality (VR) has been used in conjunction with robotics, biofeedback training, and modern multi-touch technology. In 2019, Maggio et al. [25] conducted a study of 56 participants with TBI; the experimental group underwent rehabilitation training with Lokomat Pro, equipped with a VR screen; the rehabilitation protocol consisted of a total of 40 training sessions. Ultimately, the result supported that Lokomat plus virtual reality can improve the cognitive and behavioral functions in participants with TBI. Using multitouch-multiuser tabletop (MMT) devices: Snowflake MultiTeach (MT) and Diamond Touch Table (DTT), coupled with MediqVR virtual reality (VR) platform, and

Table 3: The advantages and disadvantages of virtual reality- (VR-) based training.

Virtual reality- (VR-) based training	
Advantages	(1) More usable and cheaper tools [20, 21]. (2) Well-tolerated [24].
Disadvantages	(1) Accessibility and the cost of virtual tools [20]. (2) VR assessment protocols appear to be primarily implemented for mild TBI [20]. (3) Eye fatigue [24]

Table 4: The advantages and disadvantages of Mobile Health (mHealth) Technology.

Mobile Health (mHealth) technology	
Advantages	(1) Low-cost [27]. (2) Allowed the clinician to provide focused and personalized information [29].
Disadvantages	(1) These data represent a small sample, broader TBI population should be exercised with caution [28].

computer-based interactive applications were applied in rehabilitation design; the research found that MediqVR training improves the patients' intuition, communication and expression ability, enable them to carry out social activities naturally, and reduce the patients' social anxiety [26]. We summarized the advantages and disadvantages of virtual reality- (VR-) based training in Table 3.

2.4. Mobile Health (mHealth) Technology. TBI can lead to severe motor, cognitive, and emotional disturbance, and the rehabilitation of TBI is a long process. Fortunately, Mobile Health (mHealth) is an emerging technology, which can help to diagnose and manage patients with TBI greater.

One study explored that the effectiveness of a prospective memory assists method combining smartphones with Web-based calendars in community-dwelling patients with traumatic brain injury [27]. Patients were asked to use a windows phone- (version 7.5) based smartphone as the primary memory compensation strategy during the intervention phase, avoiding the use of existing assistive tools and strategies. A study of 13 patients received a group-based therapy for six weeks, and the result supported that the smartphone improved patients' memory problems significantly. Another study assessed compliance with an 8-week intervention daily ecological momentary assessments (EMA) conducted via a smartphone application, and the result also demonstrated the efficacy of mHealth system [28]. There are also reports of new technologies that Interactive iBook-Based Patient Education be applied to improve the self-reported measures of patient and family knowledge, and it is helpful to improve the potential anxiety and other symptoms after TBI [29]. The advantages and disadvantages of Mobile Health (mHealth) Technology are summarized in Table 4.

3. Brain-Computer Interfaces (BCI)

Brain-computer interfaces (BCI) are developing into a possible method to replace the brain's normal output pathways of peripheral nerves and muscles, and allowing paralytic patients can use a new method of communication and computer control, which has developed significantly over the past several decades [30]. Brain-computer interface (BCI) can convert brain signals obtained by noninvasive and invasive methods into control signals of some external devices, such as computer cursor or robot limb [31].

Many clinical studies confirmed the effectiveness of BCI in the rehabilitation of patients with TBI [32, 33]. Morrison et al. applied Hopfield neuronal networks to prevent the loss of memory in TBI patients by using cerebral organoids or external microelectronics, which provide a starting point for new treatment strategies [34]. In addition, the integration of brain-computer interface (BCI) and functional electrical stimulation (FES) technologies also bring better treatment [35]. Although the BCI technology has advanced significantly over the years, it still faces many challenges. These challenges mainly include signal degradation (from implanted recording electrodes), accuracy and robustness of neural decoding algorithms over time, miniaturization of the system, adverse events from using FES, and ease of use of whole system et al., so the application of BCI in TBI rehabilitation still need further exploration. We summarized the advantages and disadvantages of brain-computer interfaces (BCI) in Table 5.

4. Noninvasive Brain Stimulation (NIBS)

In the past few years, the extensive use of noninvasive brain stimulation (NIBS) technology has led to a significant development in our understanding of brain behavioral relationships [36]. As a potential treatment for neurological and psychiatric diseases, including traumatic brain injury, it has also received extensive attention [37]. NIBS mainly includes transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS).

4.1. Transcranial Direct Current Stimulation (tDCS). Transcranial direct current stimulation (tDCS) is one method of NIBS. It can increase or decrease cortical excitability according to different polarities (anode or cathode), regulate synaptic plasticity through long-term inhibition or enhancement, and promote long-term functional recovery [38]. It can provide a safe and noninvasive method for regulating neural excitability during neurorehabilitation.

In 2014, Middleton et al. [39] conduct a study, which enrolled 5 patients with chronic neurologic insult, which stroke or traumatic brain injury more than 6 months. Participants were requested to complete 24 courses (40 minutes, three times a week) of upper limb physical therapy (UE-PT) and to perform bihemispheric tDCS on the motor cortex at a speed of 1.5 MA in the first 15 minutes of each course. The result indicated that this therapy improves patients' indicators significantly. The emergence of posttraumatic disorders of consciousness (DOC) increases the mortality of patients and restricts their rehabilitation. A double-blind

Table 5: The advantages and disadvantages of brain-computer interfaces (BCI).

	Brain-computer interfaces (BCI)
Advantages	(1) Invasive BCI: High accuracy [31] (2) Increase remote access to rehabilitation supporting transition into home [32]. (3) Allows for a better control of the system as well as greater effects on brain reorganizations [33]. (4) Implantable BCIs have provided neural recordings with increased spacial resolutions [35].
Disadvantages	(1) Limited ability to represent more than two signal output choices [30]. (2) The risks and expenses associated with the surgery [31]. (3) Signal degradation (from implanted recordings electrodes), accuracy and robustness of neural decoding algorithms over time, miniaturization of the system, muscle fatigue when using FES, and overall system ease-of-use [35].

Table 6: The advantages and disadvantages of transcranial direct current stimulation (tDCS).

	Transcranial direct current stimulation (tDCS)
Advantages	(1) Relative ease of use and good safety profile [37]. (2) A safe, noninvasive technique [39]. (3) Stimulation was well-tolerated [39]. (4) It is a painless, noninvasive, easily applied, and effective therapy [40].
Disadvantages	(1) There is an ongoing debate about the precise neurophysiological processes that are stimulated by these techniques [36]. (2) They can only directly affect activity in cortical regions [36]. (3) Did not focus on possible late-occurring side effects or side (4) Effects that might be caused by intensified use [36]. (5) Lack of large-sample clinical trials [40].

RCT study has found that tDCS can effectively improve the consciousness disorder of the people with TBI [40]. The systematic review of transcranial direct current stimulation (tDCS) effects on the rehabilitation of traumatic brain injury (TBI) also supported that although tDCS has been used in clinical treatment, it still needs further improvement, and the after-effects of tDCS are mostly short lived [41]. The advantages and disadvantages of transcranial direct current stimulation (tDCS) are summarized in Table 6.

4.2. Repeated Transcranial Magnetic Stimulation (rTMS). rTMS is another noninvasion method to stimulate the human brain. It can influence brain plasticity and cortical reorganization through stimulation-induced changes in neuronal excitability, and the treatment effects of rTMS on cortical excitability depend on the stimulation parameters applied, including the stimulus intensity, frequency, and duration of stimulation [42]. The low-frequency rTMS (<1 Hz) applied at the motor threshold or slightly suprathreshold intensities result in a suppression of cortical excitability, and high-frequency (≥5 Hz) suprathreshold stimulation will lead to increased cortical excitability [43, 44].

Disorders in memory and neural behavior are a common sequence of TBI. A study shows that low-field magnetic stimulation (LFMS) improved the cognitive and motor function of TBI mice significantly. The neuroprotective effect of LFMS may be achieved through the regulation of cellular prion protein (PrPc) and/or circadian rhythm-related proteins [45]. A case report found that rTMS could improve the neural activity, to regulate the neural activity, and/or to facilitate recovery in patients with disturbance of consciousness after TBI [46]. Another study confirmed that high-frequency transcranial magnetic stimulation could reduce the pain scores of patients with TBI and improve quality of life [47]. Headache is another common symptom after TBI; Leung et al. conducted a study to test the effectiveness of rTMS in headache after TBI; the result indicated that rTMS can alleviate the headache symptom and provide a transient mood-enhancing benefit [48].

Although rTMS has been widely used in the rehabilitation of TBI, there are still a lot of areas that need to improve. There is evidence that rTMS may be led to adverse events such as seizure [49], so we should consider the safety when we use it. The advantages and disadvantages of Repeated Transcranial Magnetic Stimulation (rTMS) are summarized in Table 7.

5. Wearable-Assisted Devices

Wearable-assistive devices have been used in the rehabilitation of neurological disorder such as traumatic brain injury widely. According to the report [50], Mikołajczyk et al. carried out the research and design of the system for elbow rehabilitation which consists of a single-degree-of-freedom (SDOF) solution and a single-axis stepper motor with a controller. They designed an exoskeleton, a wearable, external structure which can support or even replace the muscle actuation in the patient, and the system promotes the rehabilitation of upper limb function after TBI. Portable electronic aids have also developed rapidly in recent years. In the study [51], we learned that portable electronic aids may improve the function of patients with TBI in the areas of learning, organization, and initiation, but its clinical application may be limited by its high price and low clinical confidence. The advantages and disadvantages of wearable-assistive devices are summarized in Table 8.

Table 7: The advantages and disadvantages of Repeated Transcranial Magnetic Stimulation.

	Repeated Transcranial Magnetic Stimulation (rTMS)
Advantages	(1) A noninvasive and painless method [42, 46]. (2) A safe, noninvasive, effective therapeutic intervention [47, 49]. (3) No significant side effects [48].
Disadvantages	(1) The most clinically effective rTMS parameters and the optimal site for stimulation in TBI are not currently known [42]. (2) The limited knowledge regarding the side effects of TMS [42]. (3) TBI patients who receive rTMS may experience a mild headache after the treatment session [42]. (4) Lead a risk of temporary mild hearing loss due to its substantial volume [42]. (5) The high intensity of stimulation is not well tolerated [48].

Table 8: The advantages and disadvantages of wearable-assistive devices.

	Wearable-assistive devices
Advantages	(1) Safety, proven efficacy [50]. (2) High cost and low clinician confidence [51].
Disadvantages	(1) Lack high-h-quality evidence to assess its effectiveness [50]. (2) The advantages and disadvantages of technology are unknown [51].

6. Discussion

In this paper, we summarized the application of interdisciplinary combination between medicine and engineering in the rehabilitation of traumatic brain injury. With the rapid development of science and technology, the interdisciplinary combination between medicine and engineering technology brings new hope to TBI patients. Artificial intelligence (AI), brain-computer interfaces (BCI), noninvasive brain stimulation (NIBS), and wearable-assistive devices have been widely used in the rehabilitation of patients with TBI; meanwhile, there are still some areas that need to improve.

First, as summarized above, we can see that the application of these technologies lacks high evidence from clinical trials, so we should conduct more clinical trials to prove their effectiveness in the future. When it comes to the application of virtual reality (VR), we must consider the limitations of it. The application of virtual reality technology in clinical practice is mainly limited by two factors: accessibility and the cost of virtual tools [20]. Additionally, Many interdisciplinary combinations between medicine and engineering technologies lack standardized treatment procedures; we should make efforts to develop the individualized, precise treatments in the future.

Secondly, clinician attitudes are important which can affect the use of any assistive technology in the training and supporting for the rehabilitation of TBI patients, so we should improve the awareness of clinician for the new rehabilitation facility. Moreover, according to report [52], traditional Chinese medicine therapy especially acupuncture and moxibustion therapy is a benefit to the rehabilitation of TBI patient; He et al. showed that early application of acupuncture gets better effects on restoration of arousal function of the brain in patients with TBI than functional electrical stimulation. So whether we can further the role of acupuncture therapy.

Data Availability

This article is a review article and does not contain relevant data.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of the paper.

Authors' Contributions

Qingyong Wang and Weibo Sun contributed equally to this work. Zhongren Sun and Dongwei Sun are both corresponding author to this work.

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Research Article

Portable 3D Gait Analysis Assessment in MTT Treat Chronic Ankle Instability: A Retrospective Study

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Purpose. Retrospective analysis of the effect of portable 3D gait analysis as an innovative evaluation method in the treatment with MTT on chronic ankle instability patient. *Methods*. From January 1, 2019, to December 31, 2019, 56 cases of chronic ankle instability (CAI) were extracted from the medical record system of Shenzhen Longhua District Central Hospital. All the patients of 56 cases accepted the medical training therapy (MTT). As outcome parameters, the alterations of the Cumberland ankle instability tool (CAIT), foot and ankle ability measure (FAAM), were used before the treatment and after treatment; meanwhile, the portable apparatus 3D gait analysis was used to measure the gait parameters. *Conclusion*. The results showed only ankle angle parameters Y-axis, maximum dorsiflexion during support period (°) had a significant difference, and the p value is 0.039. Meanwhile, the CAIT, FAAM, and most 3D gait analysis data had no significant difference. This particular statistical difference shows that CAI can be measured scientifically and objectively, although most measurement parameters have no change. These results make further reveal that the CAI patients are suffering with dynamic abnormality of ankle motion angle; this also provides us with a measurable and systematic evaluation reference plan for CAI treatment in the future.

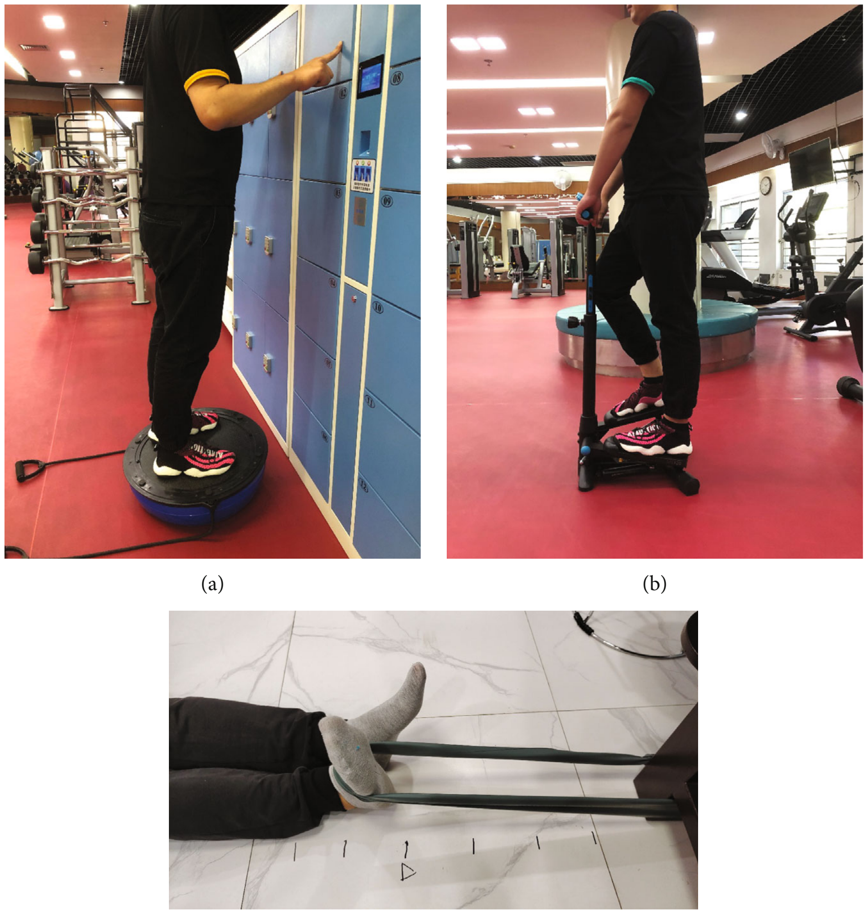
1. Introduction

Ankle sprain is one of the most common musculoskeletal injuries in physical activities. Patients with ankle sprain will suffer from decreased ankle stability and recurrent sprain several months and years after the initial ankle injury, which is the characteristic of chronic ankle instability (CAI) [1]. About 40% of the patients with first-time ankle sprain developed CAI symptoms during the 12-month follow-up, repeated sprains caused by CAI can lead to injuries of soft tissues such as ligaments and tendons of the ankle joint, and severe ankle sprains may induce ankle osteoarthritis [2]. Therefore, it is necessary to carry out correct and effective intervention or treatment. At present, the main nonsurgical intervention methods of rehabilitation medicine for CAI are exercise therapy, ankle protectors, intramuscular patches, etc. Medical training therapy (MTT) is a comprehensive medical sports rehabilitation technology, which is mainly used in sports injuries, postoperative rehabilitation, bone and joint diseases, limb motor dysfunction, pain, and other fields. Our group retrospectively analyzed the medical records of MTT of CAI, in order to further evaluate its clinical efficacy.

2. Clinical Data

2.1. Research Object. Patients with CAI who accepted MTT in the Rehabilitation Department, or Traditional Chinese Medicine Department of the Shenzhen Longhua District Central Hospital from January 1, 2019, to December 31, 2019, were extracted from the medical record system of Shenzhen Longhua District Central Hospital. Finally, according to the inclusion and exclusion criteria, a total of 56 subjects were determined.

2.2. Diagnostic Criteria. The diagnostic criteria of CAI were formulated with reference to the screening criteria of CAI proposed by the International Ankle Consortium in 2014



(a) (b) (c)

Figure 1: The 3D gait analysis: (a) the exercise training of the ankle, (b) the balance training, and (c) the resistance training.

[3]: (a) a history of at least 1 significant ankle sprain, the initial sprain must have occurred at least 12 months prior to enrollment; (b) a history of the previously injured ankle joint "giving away" and/or recurrent sprain and/or "feeling of instability"; (c) Ankle Instability Instrument (AII): answer "yes" to at least 5 yes/no questions; Cumberland ankle instability (CAIT): <24; Identification of Functional Ankle Instability (IdFAI) > 11; foot and ankle ability measure (FAAM): ADL scale < 90%, sport scale < 80%; Foot and Ankle Outcome Score (FAOS): <75% in 3 or more categories.

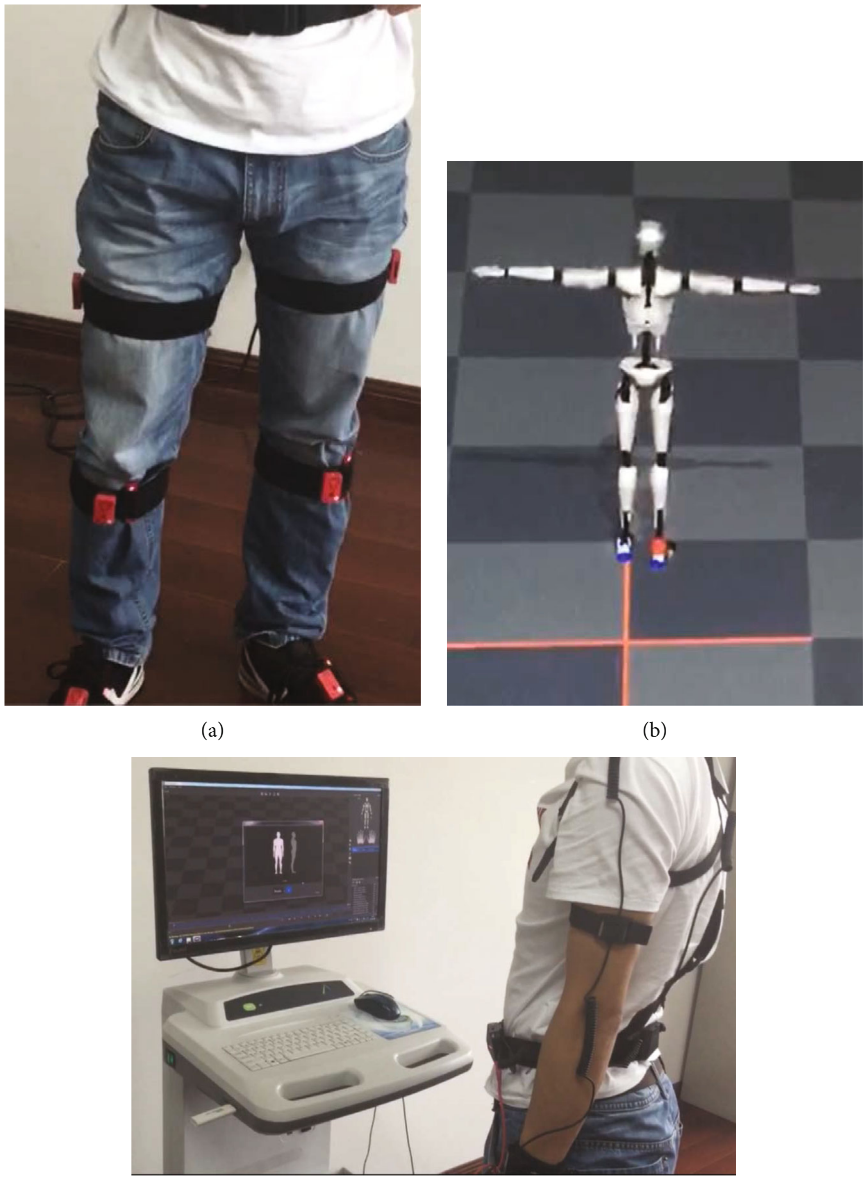
2.3. Inclusion Criteria. The inclusion criteria were as follows: (a) the diagnostic criteria above are met; (b) medical records are complete, the MTT prescription is entered at least once a week, and there are assessment scales before and after treatment; (c) the length of treatment is at least 2 weeks; (d) the contact information can meet follow-up criteria; (e) participation is voluntary, and informed consent has been signed.

2.4. Exclusion Criteria. The exclusion criteria were as follows: (a) patients with a history of lower limb fracture or surgery, or other musculoskeletal diseases; (b) patients with acute injury of lower limbs within three months; (c) the length of treatment is less than 2 weeks; (d) incomplete medical records and lack of important diagnosis and treatment information; (e) lack of contact information and inability to cooperate with follow-up.

3. Treatment

Before the first treatment, all the patients accepted the examination and evaluation of the safety of MTT by rehabilitation physicians and physiotherapists. The treatments occurred 3 times per week for 8 weeks under the supervision of physiotherapists. The procedures of the treatment are as follows:

(a) The resistance training of the ankle [4]. The training was carried out with rubber-resistance bands (DOMYOS), according to different elastic forces, it was set to four levels: red → green → blue → orange. The patients progressed to next color level biweekly. (1) Calculation of the resisting force of the training: measured the stretching distance of rubber-resistance band, and marked the point of 70% of the maximum stretching length of rubber-resistance bands on the floor. (2) The patients sat on the floor and kept their knees straight and



(a) (b)

(c)

Figure 2: The 3D gait analysis: (a) wearable biomarkers, (b) computer software modeling, and (c) movement and model action matching.

neutral. The rubber-resistance band was folded in half; one end was fixed, and the other end was wrapped around the involved foot. (3) Stretched the rubber-resistance band to the marked point only by the involved foot, then performed the training in 4 directions: inversion, eversion, plantar flexion, and dorsiflexion. Repeated 10 times in every direction for one group, 3 groups per treatment [5]

(b) The balance training of the ankle. The training was carried out with the balance training board (DOMYOS Balance Board). With the patients in an upright standing position and fingers supporting the wall, the involved foot stood in the center of the balance training board and kept balance for 40 s, then changed direction after 10 s rest. Repeated 5 times for one group, 5 groups per treatment [6]

(c) The exercise training of the ankle. The training was carried out with stair steppers (DECATHLON MS100 Stepper). Placed feet on the stair stepper to perform alternate pedaling actions. Repeated 50 times for one group, 3 groups per treatment. See Figures 1(a)–1(c)

4. Outcomes

We set 3D gait analysis data as primary outcome, and the secondary outcome was the Cumberland ankle instability tool (CAIT), foot and ankle ability measure (FAAM).

5. Evaluation

5.1. 3D Gait Analysis. Before and after treatment, we applied 3D gait analysis (Real Gait, NeuCogic Medical Co., Ltd.) to measure the gait parameters. Temporal and spatial parameters, such as stride frequency, step length, walking speed, stride length, and max ankle angles at vertical, horizontal, and coronal planes, were recorded with Portable Apparatus Real Gait [7]. Before the test, the operator calibrated the parameters of the instrument and explained the procedure of the test to the patients. After they fully understood the evaluation process, we begin to conduct a gait analysis test and get gait-related parameters [8]. For the 3D gait analysis, please see Figures 2(a)–2(c).

5.2. Cumberland Ankle Instability Tool (CAIT). Before and after treatment, CAIT questionnaire was used to evaluate the pain and stability of the ankle in patients' daily life, such as walking, running, going downstairs, standing on one leg, and turning sharply.

5.3. Foot and Ankle Ability Measure (FAAM). FAAM consists of two subscales, among which 21 items of the FAAM-ADL scale are related to activities of daily living, and 8 items of the FAAM-sport scale are related to sports.

6. Statistical Methods

The data was presented as mean and standard deviations (SD). The data was analyzed by an independent statistician with IBM SPSS Statistics 21.0. A two-sided p value of less than 0.05 was defined as statistical significance. Paired t-test was used in the data comparison between before and after treatment.

7. Results

The baseline data was listed in the following; it indicated the basis information of the patients. Please see Table 1.

The CAIT and FAAM data comparison results showed there was no significant difference between before and after treatment. Please see Table 2.

The 3D walking characteristic data comparison showed most results had no significant difference, while the "maximum dorsiflexion during support period" had the p value which was 0.039. Please see Figure 3 and Table 3.

Table 1: Baseline data.

Items	Values
N (case)	56
Mean age (y)	34.05
SD age	12.72
Female/male	31/25
Left/right	17/39
CAIT mean (score)	23.53
CAIT SD	6.04
FAAM-ADL mean (score)	95.88
FAAM-ADL SD	14.15
FAAM-sports mean (score)	72.90
FAAM-sports SD	10.22

Table 2: CAIT and FAAM score comparison between before and after treatment.

		Before treatment	After treatment	.sig
CAIT	*N* (case)	56	56	1
	Mean (score)	23.53	24.06	0.816
	SD	6.04	10.80	
	Max (score)	27	27	
	Minimum (score)	21	20	
FAAM-ADL	Mean (score)	95.88	95.91	0.902
	SD	14.15	18.55	
FAAM-sports	Mean (score)	72.90	73.03	0.561
	SD	10.22	12.16	

8. Discussion

The ankle is one of the main joints bearing gravity and ground reaction force; the feet bear the ground reaction force of 1.5 times of body weight when walking; moreover, when running, it can reach 2-3 times of body weight. Therefore, ankle sprain is one of the most common sports injuries, accounting for about 30% of them [9–11]. After ankle sprain, there may be a variety of aftereffects, including ankle instability, pain, and weakness. In view of this phenomenon, scientists have done a lot of related researches [12]. Hertel [7] defined the phenomenon of repeated instability and multiple sprains of the ankle as CAI. Recent studies have shown that the occurrence of chronic ankle instability is related to ligament injury, insufficient muscle strength, delayed muscle reaction time, and weakened ankle proprioception [13].

Medical training therapy (MTT) is one form of nonsurgical treatment advocated by guidelines, it is a sport rehabilitation system based on science and evidence, and it helps the impaired structure and function to recover comprehensively by different sport training [14]. MTT has the characteristics of planning, systematicness, and initiative; the core elements of MTT are joint flexibility, coordination, endurance, and muscle strength. MTT focuses on active exercise and combines passive exercise to encourage patients' subjective active participation. Therefore, it not only improves patients' body function but also emphasizes patients' comprehensive physical and mental rehabilitation [15, 16]. In this retrospective study, we also found that MTT can relieve the CAI patients' ankle pain and improve ankle instability.

At present, the research on CAI mainly focuses on the biomechanical mechanisms such as muscle strength, balance function, and posture stability. As gait analysis helps to describe the characteristics of the gait of CAI patients, and quantitative analysis of the biomechanical changes of the ankle, we apply it to the treatment evaluation of CAI [17, 18]. The kinematic characteristics of gait can be reflected by

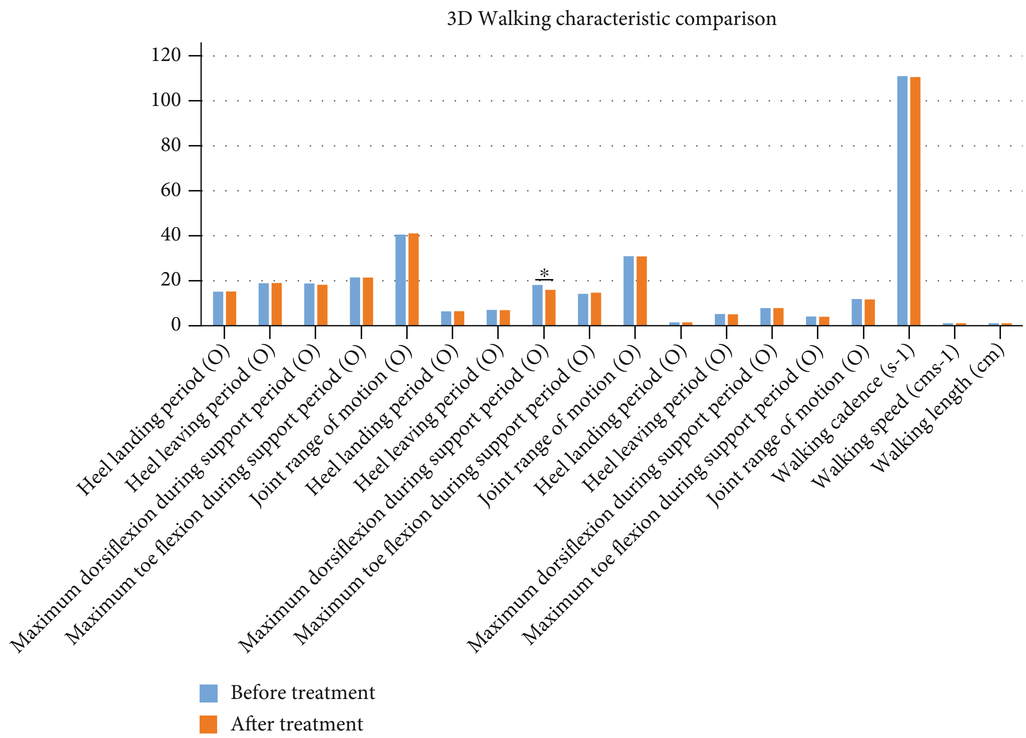


Figure 3: 3D walking characteristic mathematical absolute value comparison between before and after treatment. *sig.<0.05.

Table 3: 3D walking characteristic comparison between before and after treatment.

		Before treatment mean (SD)	After treatment mean (SD)	.sig
Ankle angle parameters *X* -axis	Heel landing period (°)	15.16 (3.71)	15.21 (4.18)	>0.05
	Heel leaving period (°)	-18.91 (4.66)	-19.02 (3.80)	>0.05
	Maximum dorsiflexion during support period (°)	18.80 (4.61)	18.19 (6.77)	>0.05
	Maximum toe flexion during support period (°)	-21.47 (3.10)	-21.45 (4.46)	>0.05
	Joint range of motion (°)	40.55 (11.85)	41.08 (8.02)	>0.05
Ankle angle parameters *Y* -axis	Heel landing period (°)	6.38 (1.03)	6.46 (1.90)	>0.05
	Heel leaving period (°)	7.05 (1.17)	6.92 (2.06)	>0.05
	Maximum dorsiflexion during support period (°)	18.14 (12.99)	15.96 (7.00)*	0.039
	Maximum toe flexion during support period (°)	-14.18 (4.95)	-14.70 (3.11)	>0.05
	Joint range of motion (°)	30.95 (8.06)	30.82 (6.90)	>0.05
Ankle angle parameters *Z* -axis	Heel landing period (°)	-1.51 (0.27)	-1.49 (0.35)	>0.05
	Heel leaving period (°)	5.22 (4.28)	5.06 (3.72)	>0.05
	Maximum dorsiflexion during support period (°)	7.82 (4.08)	7.86 (4.22)	>0.05
	Maximum toe flexion during support period (°)	4.09 (2.80)	4.01 (3.06)	>0.05
	Joint range of motion (°)	11.90 (6.67)	11.70 (5.49)	>0.05
Walking space characteristics	Walking cadence (s^{-1})	111.05 (5.04)	110.62 (6.85)	>0.05
	Walking speed (cms^{-1})	1.10 (0.09)	1.10 (0.20)	>0.05
	Walking length (cm)	1.11 (0.02)	1.11 (0.04)	>0.05

the following parameters: step length, pace, pace frequency, step width, step angle, gait cycle and the percentage of each phase in the total cycle, the movement angle and angular velocity of the three joints of lower limbs in three planes, etc. Monaghan et al. [19] analyzed the gait of patients with CAI 100 ms before landing and 200 ms after landing, and the results showed that patients with CAI had more varus than the normal group during normal walking, and the swing speed of the heel swing period was significantly faster than that of the normal group.

In this study, the CAIT and FAAM data showed no significant difference; meanwhile, the 3D gait analysis assessment showed nearly the same results; however, uniquely, the data of ankle angle parameters Y-axis and maximum dorsiflexion during support period (°) showed a significant difference when p value is 0.039. This particular statistical difference shows that CAI can be measured scientifically and objectively, although most measurement parameters have no change. These results make further reveal that the CAI patients are suffering with dynamic abnormality of ankle motion angle; this also provides us with a measurable and systematic evaluation reference plan for CAI treatment in the future.

Data Availability

The study data used to support the findings of this study are currently under embargo while the research findings are commercialized. Requests for data, 24 months after publication of this article, will be considered by the corresponding author.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Yujuan Song was the leader of the project of "high-level medical team project" and the main author in this paper; Sibai Xu, Jun Jia, and Yanqiu Dai collected data and made clinical implementation, Hebin Liu took the statistics, and Zhenjing Li did much on the English language support.

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Research Article

Customizing Robot-Assisted Passive Neurorehabilitation Exercise Based on Teaching Training Mechanism

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Passive movement is an important mean of rehabilitation for stroke survivors in the early stage or with greater paralysis. The upper extremity robot is required to assist therapists with passive movement during clinical rehabilitation, while customizing is one of the crucial issues for robot-assisted upper extremity training, which fits the patient-centeredness. Robot-assisted teaching training could address the need well. However, the existing control strategies of teaching training are usually commanded by position merely, having trouble to achieve the efficacy of treatment by therapists. And deficiency of flexibility and compliance comes to the training trajectory. This research presents a novel motion control strategy for customized robot-assisted passive neurorehabilitation. The teaching training mechanism is developed to coordinate the movement of the shoulder and elbow, ensuring the training trajectory correspondence with human kinematics. Furthermore, the motion trajectory is adjusted by arm strength to realize dexterity and flexibility. Meanwhile, the torque sensor employed in the human-robot interactive system identifies movement intention of human. The goal-directed games and feedbacks promote the motor positivity of stroke survivors. In addition, functional experiments and clinical experiments are investigated with a healthy adult and five recruited stroke survivors, respectively. The experimental results present that the suggested control strategy not only serves with safety training but also presents rehabilitation efficacy.

1. Introduction

New advances in technology and an increased upper extremity motor dysfunction lead to widespread adoption of robots in clinical rehabilitation poststroke. Robotic devices for upper extremity rehabilitation have the potential to deliver highly repetitive, task oriented, intensive, and quantifiable neurorehabilitation [1], which is perceived to be one of the most effective approaches for function restoration of the upper extremity. A 2018 Cochrane review [2] declares that robot-assisted therapy might improve activities of daily living, arm function, and arm muscle strength. Nonetheless, the effects depend upon the type of device, intensity, duration, amount of training, treatment program, and participant's residual functional ability. Aspects described above interest us to explore further in robotic devices for upper extremity rehabilitation.

The rapid development of many robotic devices has been seen during the past two decades. And the devices fall into two main classes: robots developed to compensate for lost skills (assisted devices) and robots designed to recover lost function by training (therapy devices) [3]. The main goal of the therapy devices is to assist therapists by customizing rehabilitation with high intensity, which is one of principles of stroke rehabilitation [4], while the therapy devices are categorized as end-effector-based robots and exoskeleton-type robots from a mechanical structure point of view. Meanwhile, passive, active-assisted, and active-resisted movement

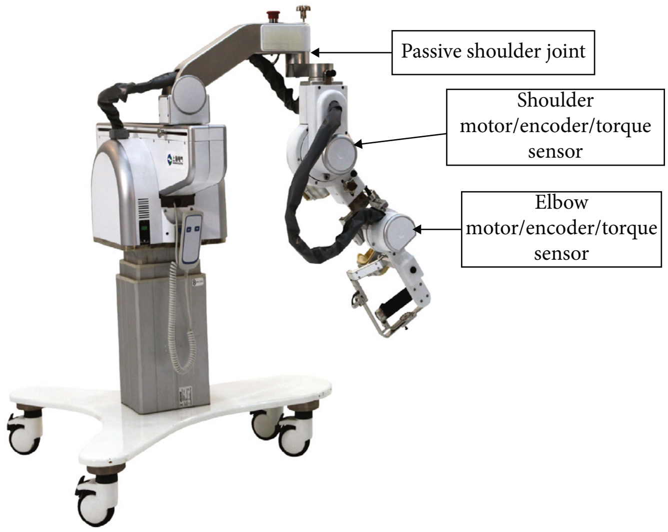

Figure 1: Mechanical structure of robot.

modes can be implemented in therapy devices and even bimanual training mode [5]. Passive movement activates the sensorimotor system through conveying proprioceptive information not only to sensory but also to motor cortices which has been well-documented [6–8]. And evidence suggests that passive movement is successfully applied in motor rehabilitation [9, 10]. The brain networks subserving passive movement in previous studies were shown in accordance with these ideas [11, 12]. Hence, rehabilitation providing passive movement is the crucial part to restoration of stroke survivors at the early stage or with greater impairment, especially for the upper extremity. Meanwhile, upper extremity robot offering passive movement is particularly urgent. However, the passive movement with motor incoordination between the shoulder and elbow appears in the upper extremity robot currently. And the movement trajectory is intermittent and deviates from the physiological activity of human due to the application of general industrial methods. Furthermore, the motor is controlled by the position merely and the upper extremity of patient follows the robot arm strictly, which contribute to the inflexibility. The robot is simply mechanical repetition. And the effect of passive movement by therapists is not achieved.

The aim of designs is not to realize a brand novel robot for stroke survivors but to fill an existing gap that customizes robot-assisted passive movement. Intending to make the passive movement patterns customized on the residual functional ability and embedded in therapist's track, the paper analyzes the design of the upper extremity robot with human-robot system and teaching training mechanism. Besides, functional and clinical experiments were conducted to verify the effectiveness and efficacy of proposed teaching training mechanisms.

Thus, the research presents a novel motion control strategy for robot-assisted passive neurorehabilitation exercise. The teaching training is developed to assist therapists with customized smoothing passive movement, based on the judgment of residual function and desired training trajectory by therapists.

2. Upper Extremity Robot Design

FELXO-Arm1 system manufactured by Shanghai Electric GeniKIT Medical Science and Technology Co., Ltd., of China is an exoskeleton robot that is kinematic equivalent to the human limb (Figure 1). In order to match natural redundancy and induce exact joint trajectories, the robot is with five degrees of freedom (DoF) to coincide with human upper extremity joints (shoulder and elbow). This feature is important to avoid mismatch undesired reaction forces that will be felt by participants as resistance to motion. There is one passive joint in the horizontal plane, while two active joints in the sagittal plane. For the passive joint in the horizontal plane, only active movement could be done by subjects. However, for the active joints of shoulder and elbow, either assistive or passive training could be provided. Active movement is done in degravity, while assisted or passive movement against gravity, which is conventional treatment by therapists for stroke survivors.

During rehabilitation training, the active joints consisting of motor and gear provide additional assistance to participants, with the encoder measuring joint angular information and the torque sensor obtaining human-robot interactive torque. We can develop different motion control algorithms to adapt different training modes based on the mechanical structure.

According to training requirement of upper extremity rehabilitation robot, the power unit on the sagittal plane of the joint is made up by a Maxon EC motor and a Harmonic Drive harmonic gear, which can provide additional 46 Nm and 13 Nm assistive torque to the shoulder and elbow joints, respectively. During training, the activity information of each degree of freedom (such as angle and angular velocity) can be measured corresponding to the encoder to control the active joint or saved in memory. The human-robot interactive force obtained by the torque sensor can be used to identify the movement intention of patient, which can improve the control precision of robot.

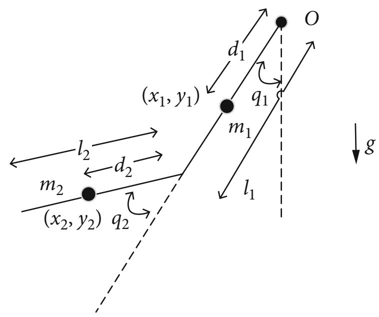

FIGURE 2: Simplified model of the human-robot system.

Our upper extremity robot has the ability to enable a strict application of motor learning principles known as stroke rehabilitation paradigms [13–17], which makes functional restoration by promoting neural plasticity and reorganization [18, 19]. Meanwhile, it makes provision of real-time sensory feedback and quantitative feedback for the participant correcting her/his movement and which is indispensable for impairment restoration [20]. Furthermore, center-out reaching of peripheral targets aimed at improving the coordination between shoulder and elbow achieves the goal-directed movement [21] during highly intensive training. The novel concept of closed-loop rehabilitation model of "central-peripheral-central" [22] is embodied during the robot-assisted rehabilitation process. Therefore, the rigorous application of motor learning principles, the goal-directed game, and the feedbacks described above make a promotion of active participation by stroke survivors, even in the passive teaching training for severely impaired [23].

2.1. Dynamic Model Analysis of Human-Robot System. Figure 2 shows the simplified human-robot coupling dynamical model in the polar coordinate system. g stands for the acceleration of gravity; m_1 represents the mass of shoulder module of robot and the shoulder of the patient. d_1 is the length from the shoulder rotation center to center of mass, l_1 is the length of upper arm of robot, and q_1 is the shoulder angle. In the same way, m_2, d_2, l_2, and q_2 represent the same values of the elbow joint.

According to the Lagrange method, the above dynamic model could be analyzed and presented in mathematical expression as the following equation:

$$\begin{aligned}\tau_1 &= \left[m_1 d_1^2 + m_2\left(L_1^2 + d_2^2\right) + 2m_2 L_1 d_2 \cos q_2\right]\ddot{q}_1 \\ &\quad + \left(m_2 d_2^2 + m_2 L_1 d_2 \cos q_2\right)\ddot{q}_2 \\ &\quad - 2m_2 L_1 d_2 \sin q_2 \cdot \dot{q}_1 \dot{q}_2 - m_2 L_1 d_2 \sin q_2 \cdot \dot{q}_2^2 \\ &\quad + (\mathrm{m_1 d_1} + \mathrm{m_2} L_1)\mathrm{g} \sin q_1 + \mathrm{m_2 g} d_2 \sin(q_1 + q_2)\tau_2 \\ &= \left(m_2 d_2^2 + m_2 L_1 d_2 \cos q_2\right)\ddot{q}_1 + m_2 d_2^2 \ddot{q}_2 \\ &\quad + m_2 L_1 d_2 \sin q_2 \cdot \dot{q}_1^2 + \mathrm{m_2 g} d_2 \sin(q_1 + q_2).\end{aligned} \tag{1}$$

τ_1 and τ_2 represent the driving moment of the shoulder and elbow, respectively.

2.2. Torque Controller. The torque control based on the position control is the global scheme of a robot controller. The robot completes the tracking of desired trajectory by introducing the feedforward controller and enhancing with a proportional differential controller. The Lagrange method-based human-robot coupling dynamical model in equation (1) is rewritten as

$$M(q)\ddot{q} + C(q, \dot{q}) + B\dot{q} + D(\dot{q}) + \mathrm{G}(q) = \tau = \tau_{\mathrm{m}} - \tau_{\mathrm{h}}, \tag{2}$$

where $\tau = [\tau_1, \tau_2]$ is the joint torque vector, $q = [q_1, q_2]$ is the joint angular position vector, $M(q)$ is the inertia matrix, $C(q, \dot{q})$ is the Coriolis force matrix, $\mathrm{G}(q)$ is the grabity vector, B is the viscous friction vector, and D is the dynamic friction vector. τ_{m} is the torque generated by the motor; τ_{h} is the interaction torque vector.

The scheme of proportional differential based on trajectory tracking controller is shown in Figure 3. According to the control scheme, we propose the control law as

$$\tau = \tau_{\mathrm{PD}}(\ddot{q}_{\mathrm{d}}, \dot{q}_{\mathrm{d}}, q_{\mathrm{d}}) + K_{\mathrm{D}}\dot{e} + K_{\mathrm{P}}e, \tag{3}$$

where $e(t) = q(t) - q_{\mathrm{d}}(t)$, $\dot{e}(t) = \dot{q}(t) - \dot{q}_{\mathrm{d}}(t)$, and K_{P} and K_{D} are proportional and differential coefficients of the proportional differential controller; the inverse dynamic term, τ_{PD} $(\ddot{q}_{\mathrm{d}}, \dot{q}_{\mathrm{d}}, q_{\mathrm{d}})$, is calculated by equation ((1)) and is the theoretical torque only. Since the torque control could enhance the smoothness significantly, it is essential to discuss the actual robot system. However, the actual robot system is determined by the frictions B and D in equation (2), which achieve the effects of torque control.

2.3. Friction Compensation. The friction compensation principle is shown in Figure 4. For the breakthrough friction i_{f_b}, compensation has occurred before the joint moves, while it cancels when the motion velocity of joint reduces to zero. d as the direction of breakthrough friction compensation is determined by the motion trend which is detected by torque sensors. The factor is set 0.9 to prevent the self-starting of the robot joint. Between the joint velocity ω and the dynamic friction torque τ_{f_k}, a mathematical model $\hat{f}(\omega)$ is necessary to be established. The model is illustrated by the following equation according to a friction modeling method [24]. The constant coefficients are $c_1 \cdots c_6$. For balancing the dynamic friction, the controller of robot identifies the parameters.

$$\tau_{f_k} = \hat{f}(\omega) = c_6 \cdot \omega + \frac{c_1 + e^{c_2\omega} - c_3}{c_4 \cdot e^{c_2\omega} + c_5}. \tag{4}$$

We calculate the frictions and gravity of robot under different positions and velocities by the proposed methods, balancing those values and improving the accuracy of the controller.

3. Teaching Training Mechanism

Neurorehabilitation, as a clinical discipline, has been established to restore upper extremity motor function poststroke basing on the ability of training and physical activity [25]. At the early stage of recovery, even for patients with severe impairment, passive rehabilitation is strongly addressed.

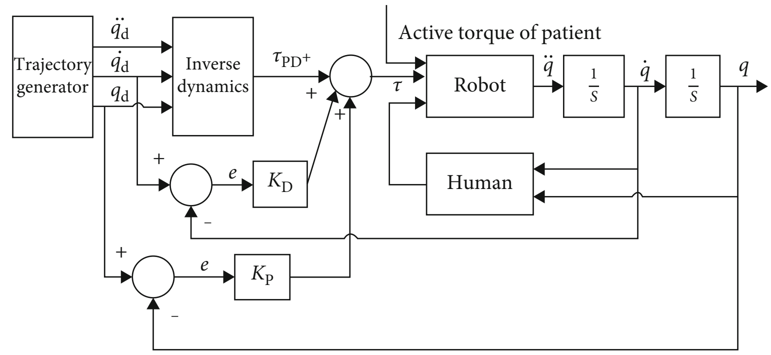

Figure 3: Structure of proportional differential-based trajectory tracking controller.

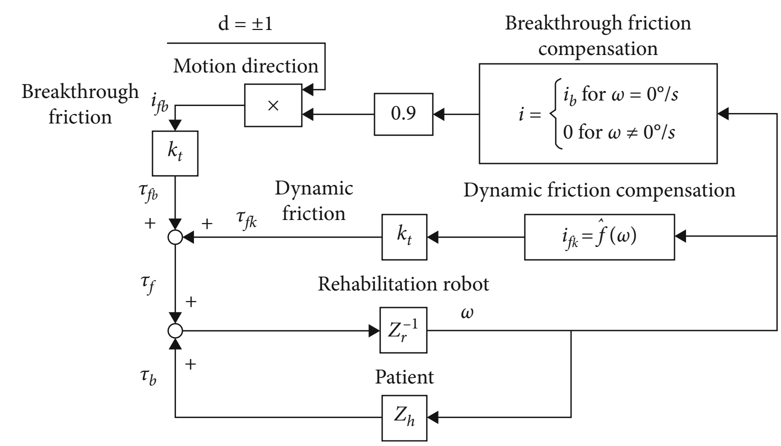

Figure 4: Schematic diagram of friction compensation.

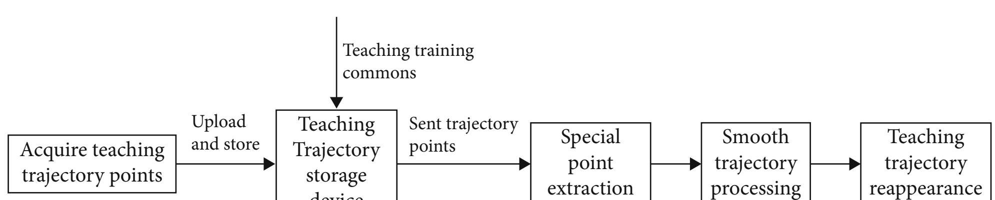

Figure 5: Teaching training control process.

However, motor incoordination between the shoulder and elbow appears in the upper extremity rehabilitation robot currently. And movement trajectory is intermittent and deviates from the physiological activity of human due to application of general industrial methods. Furthermore, the motor is controlled by position merely and the upper extremity of a patient follows the robot arm strictly, which contribute to inflexibility. In this research, teaching training mechanism is developed to conquer the weaknesses, which includes three parts (Figure 5), namely, special point extraction, smooth trajectory processing, and teaching trajectory reappearance. Therefore, flexible and smooth movement facilitates by combining motion control with torque control.

3.1. Special Point Extraction. The algorithm in Figure 6 is used to calculate the entered trajectory points during the teaching process. And then, special points of the trajectory will be output, which is processed into a smooth trajectory.

3.2. Smooth Trajectory Processing. Referring to the trajectory smoothing method and smoothing motion theory [26], the minimum joint acceleration is used in the smooth trajectory processing, with smooth and continuous variance of position, velocity, and acceleration. The trajectory function can be described by a fifth-power polynomial function in time as

$$x(t) = a_0 + a_1 t + a_2 t^2 + a_3 t^3 + a_4 t^4 + a_5 t^5. \quad (5)$$

$a_0 \cdots a_5$ are constant coefficients of polynomial function powers. The first and second derivatives of the trajectory function with respect to time are

$$\begin{aligned} \dot{x}(t) &= a_1 + 2a_2 t + 3a_3 t^2 + 4a_4 t^3 + 5a_5 t^4, \\ \ddot{x}(t) &= 2a_2 + 6a_3 t + 12a_4 t^2 + 20a_5 t^3. \end{aligned} \quad (6)$$

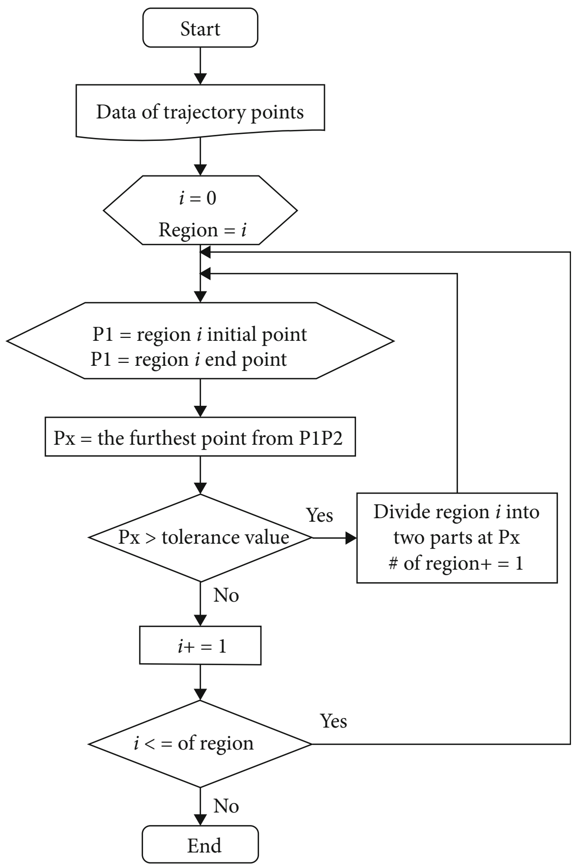

Figure 6: Special point extraction during teaching training.

According to the boundary conditions, calculate the function value of $x(t_0), \dot{x}(t_0), \ddot{x}(t_0), x(t_f), \dot{x}(t_f), \ddot{x}(t_f)$ at the boundary. t_i and t_f are at the time of beginning and ending of the trajectory. When time is normalized, the function is expressed as

$$\tau = \frac{t_f - t_0}{D}. \tag{7}$$

$\tau \in [0, 1]$, where t is the present moment, t_0 is the initial time, t_f is the final time, and $D = t_f - t_0$ and $d\tau/dt = 1/D$. The trajectory function could be rewritten as

$$\begin{aligned} x(t) &= a_0 + a_1\tau + a_2\tau^2 + a_3\tau^3 + a_4\tau^4 + a_5\tau^5, \\ \dot{x}(t) &= \frac{a_1}{D} + \frac{2a_2}{D}\tau + \frac{3a_3}{D}\tau^2 + \frac{4a_4}{D}\tau^3 + \frac{5a_5}{D}\tau^4, \\ \ddot{x}(t) &= \frac{2a_2}{D^2} + \frac{6a_3}{D^2}\tau + \frac{12a_4}{D^2}\tau^2 + \frac{20a_5}{D^2}\tau^3. \end{aligned} \tag{8}$$

The initialization condition is $x(t_0) = x_0\, \dot{x}(t_0) = v_0\, \ddot{x}(t_0) = p_0$. When $t = t_0$ and $\tau = 0$, $a_0 = x_0\, a_1 = Dv_0\, a_2 = D^2 p_0/2$. The terminal constraint condition of movement is $x(t_f) = x_f\, \dot{x}(t_f) = v_f\, \ddot{x}(t_f) = p_f$. When $t = t_f$ and $\tau = 1$,

$$\begin{aligned} a_3 &= -\frac{3D^2}{2}p_i - 6Dv_i + 10(x_f - x_i) - 4Dv_f + \frac{1}{2}D^2 p_f, \\ a_4 &= \frac{3D^2}{2}p_i + 8Dv_i - 15(x_f - x_i) + 7Dv_f - D^2 p_f, \\ a_5 &= -\frac{D^2}{2}p_i - 3Dv_i + 6(x_f - x_i) - 3Dv_f + \frac{1}{2}D^2 p_f. \end{aligned} \tag{9}$$

The point-to-point continuous and smooth trajectory will be obtained by the above calculation, including position function, velocity function, and acceleration function. The teaching training is optimized by integrating the three functions. For the upper extremity robot, the above method is applied to extract the special points of the shoulder and elbow synchronously, basing on the dynamic model analysis of the human-robot system. Therefore, the shoulder and elbow trajectories of robot are synchronous at any time. The clinical application of the human-robot system works in the kinematics trajectory, imitating the voluntary movement of the human body.

3.3. Teaching Trajectory Reappearance. The global scheme of the upper extremity robot controller is based on the torque control by introducing the feedforward controller and enhancing with the proportional differential controller. The concrete algorithm has been described above.

During clinical rehabilitation, therapists give teaching trajectory by driving the impaired upper extremity of stroke survivors, which is based on residential function and joint motion patterns expected to enhance. Then, trajectory is conducted by adjusting the position, velocity, and acceleration, tending to smoothing and consecutiveness. Therefore, the coordination teaching trajectory will reappear repeatedly with high intensity. However, the travel velocity, training duration, and intensity are changed depending on the condition of patients, which achieves patient-centered customized training by the robot.

4. Experiments and Results

4.1. Experiment Scheme. In order to verify the effectiveness and efficacy of the proposed teaching training mechanism, functional and clinical experiments were schemed. A healthy volunteer was guided to carry out the functional experiments. In functional experiments, the subject was asked to keep the arm slack when testing the teaching trajectory, feigning upper extremity weakness. Moreover, a total of five stroke survivors were recruited to undergo the clinical experiments for investigating safety and efficacy. The experimental protocol was approved by the Ethics Committee of Jing'an District Centre Hospital of Shanghai, China.

4.2. Functional Experiments. The aim of function experiments is to test the designed control system with teaching training mechanism whether providing comfortable and flowing trajectory acquired from therapists. The subject is asked to keep the tested arm slack. As described above, trajectory is determined by therapists basing on the given origin and destination. Thus, the regulation integrated the dynamic

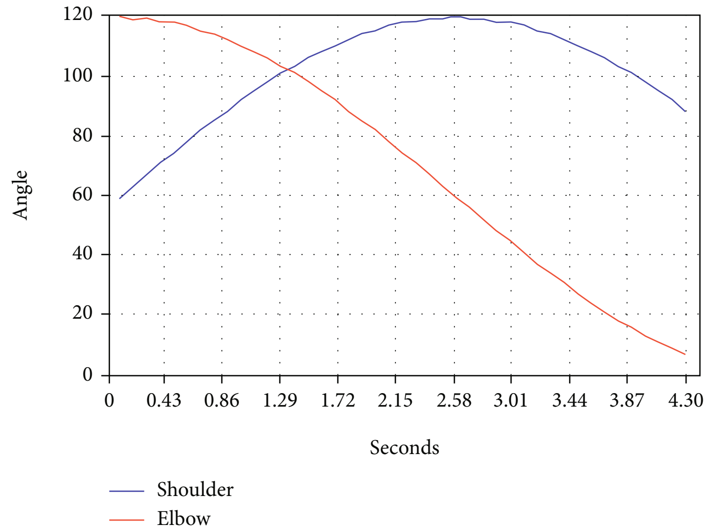

Figure 7: Teaching training trajectory. Shoulder flexion from 60 degrees in the sagittal plane to 120 degrees at 21 degrees per second along the axis of the coronal plane; Elbow flexion from 120 degrees to 8 degrees at 26 degrees per second.

Table 1: Information of stroke survivors.

Patient code	Age	Gender	Type of stroke	Days since stroke	Impaired extremity	MMSE	Fugl-Meyer SEC
S1	37	Male	CH	162	Left	30	11
S2	66	Female	CH	46	Left	24	9
S3	30	Male	CH	178	Right	29	27
S4	43	Male	CI	26	Left	26	14
S5	57	Male	CI	29	Right	25	21

CH: cerebral hemorrhage; CI: cerebral infarction; MMSE [30]: mini-mental state examination; Fugl-Meyer SEC: Fugl-Meyer assessment for shoulder, elbow, and cooperation.

model analysis of human-robot with functions of position, velocity, and acceleration. During the experiments, the corresponding information was recorded to verify the designed functions, such as the curve of trajectory, the range of shoulder or elbow, the velocity of moving, and the experience of the subject.

Figure 7 shows the trajectory. The tested upper extremity moved from shoulder flexion 60 degrees in the sagittal plane to 120 degrees at 21 degrees per second along the axis of the coronal plane, with elbow flexion 120 degrees to 8 degrees at 26 degrees per second. Hence, the teaching training of shoulder flexion with elbow extension presents the Bobath approach [27]

The approach is a classic theory for hemiplegia rehabilitation after stroke and is worthy of extensive clinical application by therapists. Additionally, no pain and discomfort occurred in the subject during the test. We tentatively suggest that this designed control strategy with the teaching training mechanism could provide effective and safe training.

4.3. Clinical Experiments. The aim of clinical experiments is to verify the effects of the proposed teaching training. Clinical experiments with five recruited stroke survivors are conducted with teaching training customized on the residual functional ability of stroke survivors during robot-assisted therapy last for four weeks (more than 3 times per week and 15 training days totally). Each survivor undergoes one session in passive training of the shoulder and elbow, 30 min per session, one training day. The program also included two-hour daily (5 days a week) sessions of physical and occupational therapy based on the paretic extremity rehabilitation and, if necessary, half an hour of speech therapy 5 times a week. Motor impairment was measured using the active range of motion (AROM) of the shoulder and elbow and the upper limb Fugl-Meyer [28] Assessment for the shoulder/elbow and coordination (Fugl-Meyer SEC) was performed before training, at midterm (after the fifth training session), and after the last session. The AROM as the sum of shoulder and elbow movements (shoulder flexion/extension, adduction/abduction, and elbow flexion/extension) was used to assess the joint excursion which could be considered correlated to spasticity [29].

The Fugl-Meyer scale measured the ability to move paretic arm, which is a global evaluation scale for impairment in stroke patients. Fugl-Meyer SEC includes items related to the movements of shoulder and elbow and the coordination. Each item is rated on a 3-point scale (maximum score, 42 points).

Demographics and clinical characteristics of five stroke survivors are presented in Table 1, with four males and one female. Subjects were between 1 month and half a year post-stroke at the time they enrolled in the study with two affected on their dominant side, while three with cerebral hemorrhage

Table 2: Subitem scores of Fugl-Meyer SEC.

Patient code	Reflex activity		Flexor synergy		Extensor synergy		Movement combining synergies		Movement out of synergy		Normal reflexes (sitting)		Coordination	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
S1	4	4	3	6	0	1	0	0	0	0	0	0	4	4
S2	4	4	2	6	1	3	0	1	0	2	0	0	2	4
S3	4	4	10	11	6	6	3	5	2	4	0	0	2	4
S4	4	4	3	12	3	5	0	5	0	3	0	0	4	4
S5	4	4	10	11	3	4	0	0	0	0	0	0	4	4

Fugl-Meyer SEC: Fugl-Meyer assessment for shoulder/elbow and coordination; Pre: pretraining; Post: posttraining.

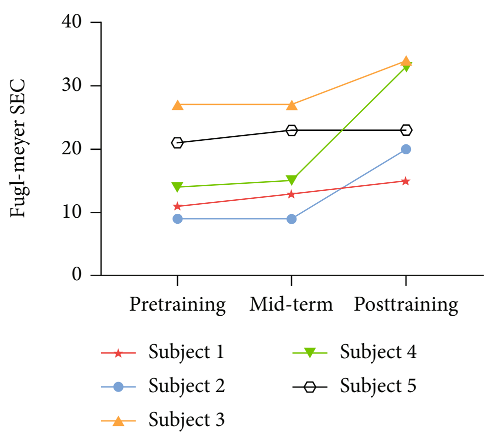

Figure 8: Compared Fugl-Meyer SEC of survivors. Fugl-Meyer SEC: Fugl-Meyer assessment for shoulder/elbow and coordination; Mid-term: after the fifth training session.

and two with cerebral infarction; the Fugl-Meyer SEC of subjects ranged from 9 to 27. All subjects exhibited moderate-to-severe deficits in movement capabilities of the paretic extremity. No other current significant impairment of the upper extremity exists in all stroke survivors, e.g., fixed contracture, frozen shoulder, severe arthritis, recent fracture, or bleeding.

All survivors regained an increased Fugl-Meyer SEC score after teaching training. Subject 1 improved in flexor and extensor synergy of the upper extremity. Subjects 2 and 4 improved in flexor and extensor synergy, movement combing, and out of synergy. Subject 3 was without improvement in extensor synergy for the ceiling effect. Subject 5 remained powerless in movement combining and out of synergy (Table 2), while subject 2 and subject 4 increased more obviously after midterm. No improvement appeared for subjects 2 and 3 before midterm. However, subject 5 reached a plateau after midterm and with the least progress (Figure 8).

The AROM of the shoulder (flexion and extension, adduction, and abduction) and elbow (flexion and extension) are displayed in Figure 9. The five stroke survivors improved AROM of flexion for the shoulder and elbow and abduction for the shoulder. However, one subject in the AROM of shoulder extension, two subjects in shoulder adduction, and four subjects in elbow extension appeared to have no improvement. Before midterm, no restoration of shoulder AROM presented for subjects 1 and 2 in flexion, subjects 2 and 5 in extension, and subjects 1, 2, and 4 in adduction. The similar situation occurred in elbow flexion for subjects 2 and 5 and extension for subjects 2, 3, 4, and 5. Nevertheless, the AROM change of shoulder extension in subject 5 and shoulder adduction in subject 1 was vacant. The variation in the AROM of elbow extension was unique during training, with only subject 1 benefitting from the teaching training and other subjects maintaining. Despite the fact that the effectiveness is not for all subjects, no adverse events and unsatisfactory events occurred during robot-assisted teaching training. No trajectory against kinematics of the human body appeared during experiments.

5. Conclusion and Discussion

The artificial intelligence and the technological revolution seem to indicate a greater artificial cognitive agents in our clinical practice, especially in rehabilitation poststroke. Robot-assisted therapy for upper extremity rehabilitation with effective scientific protocol achieves motor function recovery. Passive training with the upper extremity robot is crucial for stroke survivors with greater impairment of the upper extremity who have difficulty moving actively and even at the early stage. In the investigation, a control strategy with the teaching training mechanism was proposed to realize customized passive neurorehabilitation exercise, serving with safety and efficacy robot-assisted motion. The teaching training was developed to assist therapists by supplying customized passive training, ensuring coordination and smoothness of upper extremity motor. Meanwhile, the robot-assisted teaching training offers passive training sufficiently and alleviates the shortage of therapists.

The teaching trajectory motion keeps shoulder and elbow movements synchronized and coordination during the course of repeated movements, resolved with position and torque controlling simultaneously. Meanwhile, the model of the human-robot system is adopted to extract special points, avoiding the violation of upper extremity normal movement. Furthermore, the subject could resist the detailed movement by arm strength to realize the flexibility and plasticity of movement, with no need to follow the trajectory strictly.

The functional experiments and clinical experiments were schemed and investigated with a healthy adult and five recruited stroke survivors, respectively. In the functional

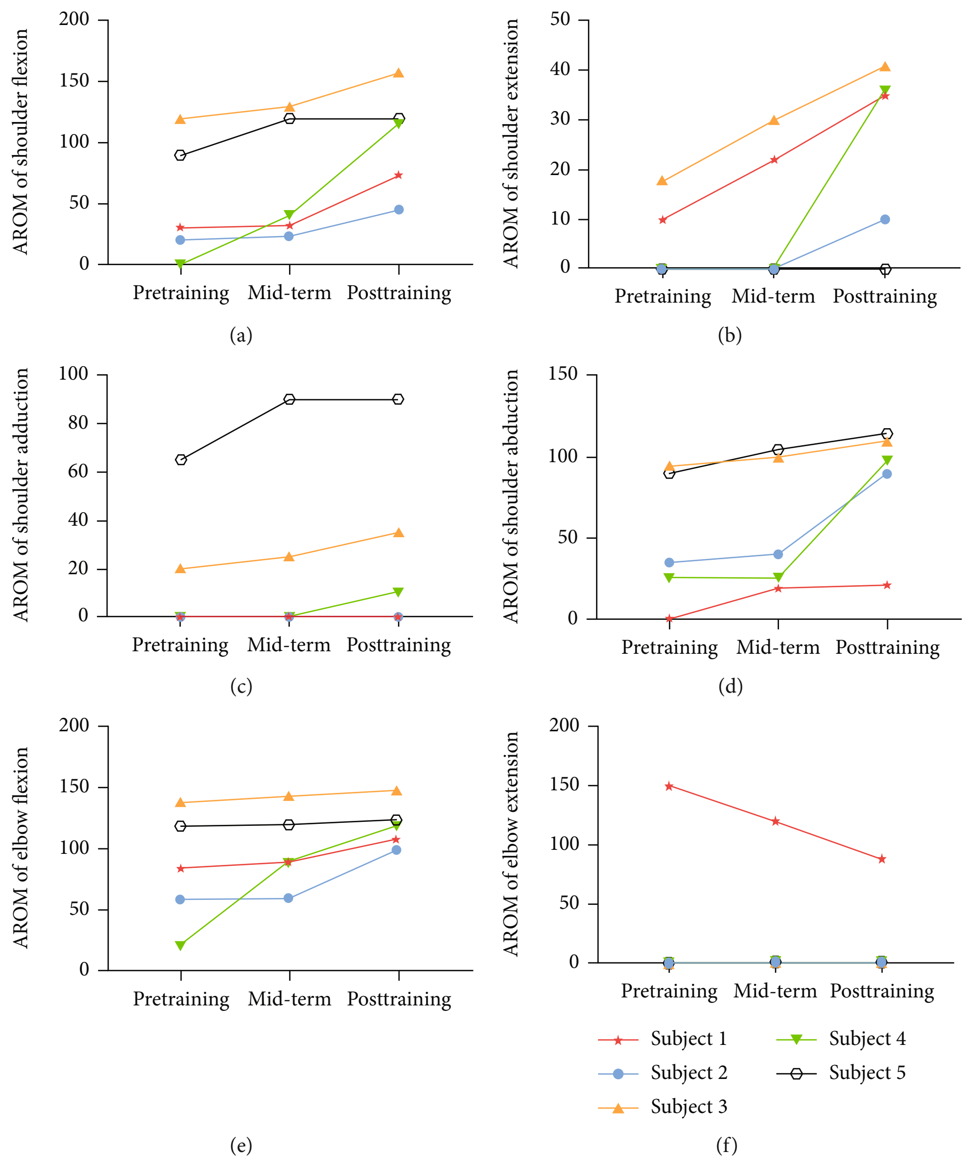

FIGURE 9: Compared AROM of the shoulder and elbow. AROM: active range of motion; Mid-term: after the fifth training session.

experiment, the repetitive passive training effectively inhibits the formation of joint adhesions, inducing the impairment of range of joint movement. In addition, the teaching training showed a smooth and coordinating curve based on the Bobath approach. The trajectory is used to suppress abnormal pattern by correcting the upper extremity flexor spasticity, while improving joint mobility and activities of daily living. During clinical experiments, the upper extremity function was evaluated by the Fugl-Meyer SEC and AROM of the shoulder and elbow. The improvement of upper extremity functional evaluation by the Fugl-Meyer SEC unfolds the restoration of the upper extremity function by robot-assisted teaching training. However, not all subjects achieve remission on the AROM of the shoulder and elbow, especially in extension. The outcomes are coinciding with the impairment of stroke. The experimental results showed that the suggested control strategy not only serves with safe teaching training but also presents rehabilitation efficacy. Due to the small sample size, the result should be cautiously considered.

Therefore, the developed teaching training mechanism played an important role to serve subjects with customized training, as closely as what the therapist did. The trajectory is made by therapists based on the residual function, ensuring adherence to the principle of human kinematics. Future models should be updated according to the clinical demands. Beyond the shoulder and elbow joints, the wrist and fingers are a nonnegligible fraction of the upper extremity function. A robot integrating shoulder, elbow, wrist, and fingers with human anatomy mechanics is indispensable in clinical rehabilitation. So it is worth investigating in future studies. On top of this, the customization of active and assistive models during robot-assisted training is equally important, which makes the robot an ideal therapist. And further study will investigate the rehabilitation efficacy with controlled experiments.

Data Availability

The data that support the findings of the study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors declare no conflict of interests on the publication of the article and the funding that they have received.

Authors' Contributions

Qingming Qu has equal contribution as the first author.

Acknowledgments

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Retraction

Retracted: Handgrip Strength-Related Factors Affecting Health Outcomes in Young Adults: Association with Cardiorespiratory Fitness

BioMed Research International

Received 8 January 2024; Accepted 8 January 2024; Published 9 January 2024

This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope

(2) Discrepancies in the description of the research reported

(3) Discrepancies between the availability of data and the research described

(4) Inappropriate citations

(5) Incoherent, meaningless and/or irrelevant content included in the article

(6) Manipulated or compromised peer review

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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[1] M. Zhou, F. Zha, Y. Chen et al., "Handgrip Strength-Related Factors Affecting Health Outcomes in Young Adults: Association with Cardiorespiratory Fitness," *BioMed Research International*, vol. 2021, Article ID 6645252, 10 pages, 2021.

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https://doi.org/10.1155/2021/6645252

Research Article

Handgrip Strength-Related Factors Affecting Health Outcomes in Young Adults: Association with Cardiorespiratory Fitness

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Objectives. Handgrip strength (HS) is a risk factor of all-cause mortality and cardiovascular diseases. However, the influencing factors and mechanisms contributing to this correlation remain unclear. Therefore, we aimed to explore factors related to HS and investigated the mechanism underlying its risk predictive value. *Methods*. This was a prospective, cross-sectional study. One hundred forty-five participants were recruited from December 2019 to November 2020. HS was measured using a hydraulic hand dynamometer and adjusted for body mass index (HS_{BMI}) and body surface area (HS_{BSA}). Body composition was assessed via bioimpedance spectroscopy. Physical fitness was measured using a cardiopulmonary exercise test system. Univariate, multiple linear regression analyses and receiver operator characteristic curve (ROC) were conducted to evaluate the associations between various participant characteristics and HS. *Results*. The average participant age was 21.68 ± 2.61 years (42.8% were male). We found positive correlations between HS_{BMI}/HS_{BSA} and VO_{2max}, VE_{max}, $Load_{max}$, and MET_{max} in both sexes ($p < 0.05$). Lean-tissue, protein, total water, and inorganic salt percentages were positively correlated, and fat percentage was negatively correlated with HS_{BMI} in men and with HS_{BMI} and HS_{BSA} in women ($p < 0.05$). Multiple regression revealed that VO_{2max} was independently associated with HS_{BSA} in both sexes ($\beta = 0.215$, 0.173; 95%confidence interval [CI] = 0.032 – 0.398, 0.026-0.321; $p = 0.022$, 0.022, respectively) and independently associated with HS_{BMI} in women ($\beta = 0.016$, 95%CI = 0.004 – 0.029, $p = 0.011$). ROC analysis showed that HS_{BMI} and HS_{BSA} can moderately identify normal VO_{2max} in men (area under curve [AUC] = 0.754, 0.769; $p = 0.002$, 0.001, respectively) and marginally identify normal VO_{2max} in women (AUC = 0.643, 0.635; $p = 0.029$, 0.042, respectively). *Conclusions*. BMI- and BSA-adjusted HS could serve as indicators of physical health, and HS_{BSA} may moderately reflect cardiorespiratory fitness levels in healthy young adults, particularly in males. Clinical trials registry site and number: China Clinical Trial Center (ChiCTR1900028228).

1. Introduction

Handgrip strength (HS) is a simple measurement and a useful indicator of physical strength. HS has been found to be strongly correlated with maximum upper and lower body strength and overall muscle strength [1]. Therefore, HS is commonly used to evaluate sports performance in athletes [2]. In addition, HS is a risk factor for unfavorable health outcomes and is associated with all-cause mortality and cardiovascular diseases (CVD), not only in older individuals but also in young adults [3–5]. Low HS (defined as <26 kg for men and <16 kg for women) is significantly correlated with a high risk of premature mortality, an increased incidence of disability, prolonged length of stay after hospitalization or surgery [6], and high risk of cancer [7]. Therefore, HS measurement can provide abundant information for health assessments [8]. However, the factors or mechanisms underlying the association between HS and health outcomes remain unclear [9].

Previous studies have shown that HS depends on age, sex, body size, socioeconomic status, and physical activity levels [10, 11]; malnutrition and sarcopenia can significantly affect HS [12]. However, these factors are insufficient in explaining the health assessment and risk prediction value of HS. Furthermore, these factors lead to a high heterogeneity of HS between different populations and create difficulty in drawing comparative conclusions among them. Therefore, to more effectively identify HS-related factors affecting health outcomes, HS adjusted for body mass index and body surface area (HS_{BMI}/HS_{BSA}) has been used to reduce the influence of heterogeneity on the results [13].

VO_{2max}, a representation of cardiorespiratory fitness (CRF), is closely correlated to physical health. Low VO_{2max} is recognized as a strong and independent risk factor for all-cause mortality, CVD [14], diabetes mellitus [15], and neoplasia [16] in healthy adults, and accordingly, VO_{2max} was consistent with HS affecting health outcomes in healthy population [17, 18]. A recent study indicated a strong association between HS and VO_{2max} in paraplegic men [12]. Therefore, we speculate that HS and CRF may be correlated with each other, thereby interactively affecting the health outcomes in the general population. The aforementioned factors may influence HS and contribute to the risk predictive value of HS. The aim of this study was to explore the potential indicators associated with HS, especially the possible interrelationships between HS and CRF.

2. Materials and Methods

2.1. Study Design. This was a prospective, cross-sectional study. This study is part of the "Study for the application value of grip strength on the unaffected side in patients with stroke", which involves two steps. The first step is to explore the correlation between HS and CRF in healthy young adults, the aim of the current study. The next step is to test whether the association between grip strength and cardiorespiratory fitness persists in stroke patients, which will be undertaken in the future. Our overall goal is to extrapolate the associations found in healthy young adults to stroke patients and to provide a useful predictive tool for stroke patients who have difficulty undertaking cardiopulmonary exercise tests. In the current study, the data were obtained from the rehabilitation center of Shenzhen Second People's Hospital and Shenzhen Dapeng New District Nan'ao People's Hospital, Shenzhen City, China. This study conforms to the standards of the Declaration of Helsinki, was approved by the Ethics Committee of Shenzhen Second People's Hospital (KS20191119005), and was registered at the China Clinical Trial Center (ChiCTR1900028228).

2.2. Participants. Study participants were recruited using a convenience sample of young adult interns in the hospital. Based on the sample size calculation method for a multiple regression study (https://www.danielsoper.com), a minimum sample size of 70 participants of each sex was needed to achieve 90% power and to detect an effect size (Cohen's f^2) of 0.26 attributable to 5 independent variables using an F-Test (multiple regression analysis) with a significance level (alpha) of 0.05. Combined with a 10% shedding rate, 154 subjects were needed for this study. The participants were recruited from December 2019 to November 2020 based on the following inclusion and exclusion criteria. The inclusion criterion was healthy young adults (aged 18–24 years) with a stable physical condition. The exclusion criteria were (1) congenital heart disease, (2) history of cardiac arrest, (3) neurological or muscular disorders, (4) fever or infection, and (5) allergy to electrode pads. Before data collection, participants were informed of the objectives and methodology of the study, and written informed consent was obtained. Tea or coffee was prohibited for at least 3 h before the tests. Tests were performed in an evaluation room with a temperature of 22–25°C. Except for scientific purposes, personal information and experimental data were kept strictly confidential.

2.3. Variables. Data for the following parameters were recorded within 72 hours after admission (baseline): (1) demographic factors, such as sex and age (years); (2) anthropometric factors, such as height (m), weight (kg), body mass index (BMI, kg/m^2), body surface area (BSA), and resting heart rate (HR_{rest}, bpm); (3) body composition, including lean-tissue percentage (%), fat percentage (%), protein percentage (%), total water percentage (%), and inorganic salt percentage (%); (4) physical fitness, including AT (ml/kg·min), VO_{2max} (ml/kg·min), HR_{rest} (rpm), HR_{AT} (rpm), HR_{max} (rpm), RER_{max}, VE_{max} (ml/min), $Load_{max}$ (W), $Psys_{max}$ (mmHg), $Pdia_{max}$ (mmHg), MET_{max}, $\Delta VO_2/\Delta Load$, ventilatory equivalent for carbon dioxide (VE/VCO_2), and oxygen uptake efficiency slope (OUES); and (5) living habits, such as smoking status (current smoker or nonsmoker) and exercise habits (sedentary, exercise 1–2 times a week, exercise ≥3 times a week). BMI was calculated as body weight/height in meters squared (kg/m^2). BSA was calculated using Mosteller formula $[\mathrm{BSA}(\mathrm{m}^2) = \sqrt{\mathrm{heigth(cm)} \times \mathrm{weigth(kg)}/3600}]$ [19]. HR_{rest} was calculated as the average heart rate during 10 min of quiet sitting. Body compositions were measured using a body bioimpedance spectroscopy (X-one; Youjiu, Shanghai, China). Physical fitness was measured via a cardiopulmonary exercise test (CPET) evaluation system (MasterScreen; Ergoline, Germany).

2.4. Handgrip Strength Test. HS was measured using a hydraulic hand dynamometer (Jamar, 1516801, Patterson Medical Ltd, UK). Based on previous authoritative research [20], the standard measurement process for HS is described as follows. The participants were seated upright with their elbow flexed at a 90°angle, with the forearm facing forward and resting on a table or an armrest. After taking the hand dynamometer, the participants were asked to complete a maximal handgrip effort two or three times on each side, expressed in absolute units (kg). Each measurement was completed at least 1 min apart to allow full muscle strength recovery. The average value of each measurement was recorded as the normal HS of one side (HS_{left} and HS_{right}), and the mean of the right- and left-side values was recorded as the average HS ($HS_{average}$). HS is partly associated with body size [21]; therefore, to prevent this association from influencing the results, we adjusted the $HS_{average}$ for BMI and BSA and created two new indicators, HS_{BMI} and HS_{BSA}, respectively.

2.5. Cardiopulmonary Exercise Test. In accordance with the "Clinician's Guide to Cardiopulmonary Exercise Testing in Adults: A Scientific Statement from the American Heart Association" [22], the graded, symptom-limited maximal cardiopulmonary exercise test (CPET) was used to measure CRF via an incremental cycle ergometer (MasterScreen; Ergoline, Germany). CRF is reflected by maximum level of oxygen consumption (VO_{2max}) [5]. Gas exchange measurements were conducted through breath-by-breath analysis using the Jaeger Carefusion system (V-706575; Jaeger, Germany). Heart rate was monitored throughout testing via a 12-lead electrocardiogram (ECG). Before testing, participants were instructed to rest for 10 min. Subsequently, participants were instructed to sit on the cycle ergometer and were fitted with a face mask, ECG, and sphygmomanometer. Then, they were instructed to complete the following measurement processes: (1) 3 min phase of seated rest, (2) 3 min phase of cycling without resistance, (3) 8–12 min phase of cycling with an increasing work rate from zero to their individual peak power (the cycling work rate was increased by one-tenth of the predicted maximum power calculated by the machine according to age, sex, height, and weight), (4) 3 min recovery period at a constant power of 20 W, and (5) 3 min phase of seated recovery. During the entire cycling period, the participants were asked to cycle at a constant speed of 60 rpm.

Oxygen uptake at maximum load was recorded for each participant as VO_{2max} (ml/kg·min). According to previous studies [23], in male young adults (15 to 30 years old), $VO_{2max} < 30$ ml/kg · min is defined as abnormal, and $VO_{2max} \geq 30$ ml/kg · min is normal. In female young adults, $VO_{2max} < 25$ ml/kg · min is regarded as abnormal, and $VO_{2max} \geq 25$ ml/kg · min is normal. The anaerobic threshold (AT) was determined by the V-slope and ventilatory equivalents methods [5]. AT is the departure point of VO_2 from a line of identity drawn through a plot of VCO_2 versus VO_2 in the V-slope method, as well as the point at which a systematic increase in the ventilatory equivalent for oxygen (VE/VO_2) occurs without an increase in the VE/VCO_2 in the ventilatory equivalent method [24]. The results of the V-slope method and ventilatory equivalents method were cross-referenced to make the final determination of AT. OUES is calculated by the equation $VO2 = a \log_{10} VE + b$ (a as OUES), which can reflect the linear relationship between logarithmically transformed VE and VO_2 [25]. During the testing period, if dizziness, chest tightness, or syncope occurred, the test was stopped immediately, the participant was transferred to a supine position, and a rescue process was initiated, if necessary. Tests were conducted by two experienced physicians who underwent standardized training.

2.6. Statistical Analyses. Continuous variables with a normal distribution are expressed as mean ± standard deviation (SD). Categorical variables are expressed as frequency or percentage. The sample size was calculated based on the recorded numbers and reference to an earlier study [26]. Participants with missing important data (e.g., HS, VO_{2max}) were excluded from the final analysis. Secondary indicators that were partially missing were filled in with a mean value. The correlation between HS_{BMI} and HS_{BSA} and other characteristics were analyzed by Pearson or Spearman analysis. Multivariate linear regression analysis was conducted to explore factors independently correlated with HS_{BMI} and HS_{BSA}. To avoid potential multicollinearity, once a variable had been used to adjust for other variables, it was not included as a covariate in the multivariate linear regression analysis. The receiver operating characteristic curve (ROC) was used to investigate the relationship between sensitivity and specificity. The optimal cutoff scores of HS_{BMI} and HS_{BSA} were determined as the score with the highest sum of sensitivity and specificity. The area under the curve (AUC) was calculated to identify the discrimination potential of HS_{BMI} and HS_{BSA} cutoff score in normal VO_{2max}. Because male and female young adults differ substantially in terms of muscular fitness and CRF, statistical analyses were performed separately to analyze the different variables related to HS_{BMI}/HS_{BSA} in the two sexes. Analyses were performed using SPSS version 21.0 (Armonk, NY: IBM Corp.). Figures were processed using GraphPad Prism version 6.01 (San Diego, USA). Two-sided p values < 0.05 were considered statistically significant.

3. Results

3.1. Characteristics of Selected Participants. The study flowchart is shown in Figure 1. In the present study, 156 healthy young adults were screened for potential eligibility. After excluding subjects with fever ($n = 2$), arrhythmia ($n = 1$), refusal ($n = 3$), and missing important data ($n = 5$), 145 (62 male, 83 female) healthy, Chinese young adults (average age 21.68 ± 2.61 years) were included for the final data analysis. Basic and anthropometric-related characteristics of the included participants are summarized in Table 1. Results showed that HS-related factors (HS_{left}, HS_{right}, and $HS_{average}$), body composition-related factors (lean-tissue percentage, protein percentage, total water percentage, and inorganic salt percentage) and CRF-related factors (VO_{2max}, VE_{max}, $Load_{max}$, and MET_{max}) in males were much higher than those in females ($p < 0.05$). Conversely, the fat percentage and resting heart rate in males were much lower than those in females ($p < 0.05$), indicating that muscular fitness, body composition, and CRF were much different between male and female young adults in this study. Therefore, it was necessary to analyze male and female participant data separately.

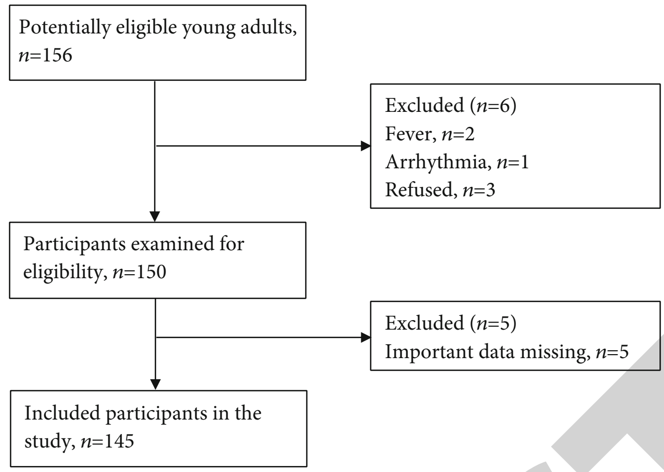

Figure 1: Study flowchart.

3.2. Univariate Correlations among Characteristics with HS_{BMI} and HS_{BSA}. The results of the correlation analysis are presented in Table 2. In young male adults, body composition including lean-tissue percentage, fat percentage, protein percentage, total water percentage, inorganic salt percentage, and CRF-related factors (VO_{2max}, VE_{max}, $Load_{max}$, and MET_{max}) were all significantly correlated with HS_{BMI} and HS_{BSA} ($p < 0.05$). In young female adults, body composition, including lean-tissue percentage, fat percentage, protein percentage, total water percentage, and inorganic salt percentage, were all significantly correlated with HS_{BMI} ($p < 0.05$). Furthermore, CRF-related factors (VO_{2max}, VE_{max}, $Load_{max}$, and MET_{max}) were all significantly correlated with HS_{BMI} and HS_{BSA} ($p < 0.05$). These results reflected that HS_{BMI} and HS_{BSA} were associated with various health-related indicators and had the potential to reflect overall health conditions.

3.3. Multiple Regression Analysis among Characteristics with HS_{BMI} and HS_{BSA}. Multivariate linear regression analysis was performed to analyze the independent association among HS_{BMI}, HS_{BSA} with anthropometric variables, and CRF-related variables. Based on the results of the univariate correlation analysis, having excluded factors of collinearity, the dominant factors correlated with HS_{BMI} and HS_{BSA} were selected into the multivariate linear regression. As shown in Table 3, in males, fat percentage was negatively associated with HS_{BMI} independently ($\beta = -2.712$, $95\%CI = -5.349 - -0.075$, $p = 0.044$), and VO_{2max} was positively associated with HS_{BSA} independently ($\beta = 0.215$, $95\%CI = 0.032 - 0.398$, $p = 0.022$). In females, VO_{2max} was positively associated with both HS_{BMI} and HS_{BSA} independently ($\beta = 0.016$, 0.173; $95\%CI = 0.004 - 0.029$, 0.026-0.321; $p = 0.011$, 0.022).

3.4. Linear Regression Analysis of HS_{BMI} and HS_{BSA}. The results of the linear regression analysis are presented in Figure 2. In male participants, HS_{BMI} explained 20.7% of the variance of VO_{2max} ($R^2 = 0.207$, $p < 0.001$), and HS_{BSA} explained 21.4% of the variance of VO_{2max} ($R^2 = 0.214$, $p < 0.001$). While in female participants, HS_{BMI} explained 5.9% of the variance of VO_{2max} ($R^2 = 0.059$, $p = 0.027$), and HS_{BSA} explained 7.1% of the variance of VO_{2max} ($R^2 = 0.071$, $p = 0.015$).

3.5. Receiver Operating Characteristic (ROC) Analysis of HS_{BMI} and HS_{BSA}. The results of ROC analysis are presented in Figure 3. In male participants, the optimal cutoffs in HS_{BMI} and HS_{BSA} used to distinguish a normal level of VO_{2max} were 2.17 and 33.83 (sensitivity = 40%, 80%, respectively; specificity = 100%, 70.6%, respectively), with an area under the curve (AUC) of 0.754 and 0.769 ($p = 0.002$, 0.001, respectively). In female participants, the optimal cutoffs in HS_{BMI} and HS_{BSA} used to distinguish a normal level of VO_{2max} were 1.17 and 15.86 (sensitivity = 66.0%, 56.6%; specificity = 63.3%, 70.0%, respectively), with an AUC of 0.643 and 0.635 ($p = 0.029$, 0.042, respectively).

4. Discussion

In this study, we explored factors associated with HS to identify potential mechanisms underlying health outcomes in healthy young adults. Our results indicated that several types of health-related factors, including body composition, physical fitness, and CRF, were correlated with HS_{BMI} and HS_{BSA}. Multivariate regression analysis revealed that VO_{2max} was independently associated with HS_{BSA} in both male and female young adults. These findings confirm HS as an indicator of physical health and reveal the possible mechanism underlying the risk predictive value of HS.

HS is affected by many demographic factors, such as age, sex, and BMI. The highest HS scores typically occur between the ages of 24 and 39 years. During normal aging, HS will decrease due to changes in anabolic resistance and reduced physical activity participation [27]. Riviati et al. found that being older than 75 years was associated with lower HS [12]. Besides, Khalid et al. revealed that BMI was positively correlated with HS [28]. Therefore, to eliminate the age-related effects, a population with a narrow age range was selected for the current study. And HS was adjusted for BMI and BSA to allow comparative analyses according to different body weights or sizes.

Table 1: Characteristics of the study participants.

Characteristics	Male ($n = 62$)	Female ($n = 83$)	p value
Demography	Mean ± SD	Mean ± SD	
Age (years)	22.01 ± 3.06	21.44 ± 2.21	0.217
Height (cm)	172.37 ± 6.95	161.05 ± 5.52	≤0.001
Weight (kg)	64.87 ± 10.06	52.64 ± 7.51	≤0.001
BMI (kg/m^2)	21.80 ± 3.05	20.20 ± 2.31	≤0.001
BSA (m^2)	1.76 ± 0.15	1.53 ± 0.12	≤0.001
HS			
HS_{left} (kg)	42.56 ± 7.02	24.29 ± 4.53	≤0.001
HS_{right} (kg)	42.81 ± 7.72	24.78 ± 4.95	≤0.001
$HS_{average}$ (kg)	42.69 ± 6.98	24.54 ± 4.39	≤0.001
HS_{BMI}	1.99 ± 0.41	1.23 ± 0.24	≤0.001
HS_{BSA}	24.38 ± 4.17	16.05 ± 2.71	≤0.001
Anthropometry			
Lean-tissue percentage (%)	0.74 ± 0.04	0.68 ± 0.03	≤0.001
Fat percentage (%)	0.22 ± 0.06	0.28 ± 0.03	≤0.001
Protein percentage (%)	0.17 ± 0.01	0.16 ± 0.01	≤0.001
Total water percentage (%)	0.57 ± 0.03	0.52 ± 0.03	≤0.001
Inorganic salt percentage (%)	0.05 ± 0.01	0.05 ± 0.01	≤0.001
Cardiorespiratory fitness			
AT (ml/kg·min)	18.78 ± 4.72	15.23 ± 3.43	≤0.001
VO_{2max} (ml/kg·min)	33.38 ± 6.28	26.49 ± 4.25	≤0.001
HR_{rest} (rpm)	80.76 ± 14.60	88.66 ± 12.84	≤0.001
HR_{AT} (rpm)	123.97 ± 15.57	126.22 ± 15.66	0.392
HR_{max} (rpm)	174.10 ± 17.49	173.57 ± 12.89	0.841
RER_{max}	1.25 ± 0.12	1.23 ± 0.17	0.317
VE_{max} (ml/min)	75.63 ± 19.55	51.77 ± 11.56	≤0.001
$Load_{max}$ (W)	179.79 ± 33.28	109.89 ± 16.83	≤0.001
$Psys_{max}$ (mmHg)	167.24 ± 26.50	138.94 ± 17.40	≤0.001
$Pdia_{max}$ (mmHg)	74.85 ± 13.28	69.00 ± 11.90	0.007
MET_{max}	9.54 ± 1.79	7.57 ± 1.22	≤0.001
$\Delta VO_2/\Delta Load$	10.31 ± 1.26	10.24 ± 1.23	0.741
VE/VCO_2	24.17 ± 3.38	27.27 ± 3.16	≤0.001
OUES	2224.47 ± 475.02	1647.63 ± 1437.16	≤0.001
Smoking* N (%)	49 (79.0)	79 (95.2)	0.003
Exercise habits* N (%)			≤0.001
Sedentary	29 (46.8)	65 (78.3)	
1–2 times a week	20 (32.3)	17 (20.5)	
≥3 times a week	13 (21.0)	1 (1.2)	

SD: standard deviation; BMI: body mass index; BSA: body surface area; HS_{left}: handgrip strength of the left hand; HS_{right}: handgrip strength of the right hand; HS_{max}: maximum handgrip strength of the two hands; $HS_{average}$: average handgrip strength of both hands; HS_{BMI}: $HS_{average}$ adjusted for BMI; HS_{BSA}: $HS_{average}$ adjusted for BSA; AT: anaerobic threshold; VO_{2max}: max oxygen uptake; HR_{rest}: resting heart rate; HR_{AT}: heart rate at anaerobic threshold; HR_{max}: max heart rate; $Load_{max}$: max work load; RER_{max}: respiratory exchange ratio at max work load; VE_{max}: minute ventilation at max work load; $Psys_{max}$: systolic pressure at max work load; $Pdia_{max}$: diastolic pressure at max workload; MET_{max}: metabolic equivalent at max work load; $\Delta VO_2/\Delta Load$: oxygen required at each load; VE/VCO_2: the minute ventilation/carbon dioxide production slope; OUES: oxygen uptake efficiency slope. Values are shown as mean ± SD or as number (%).

Table 2: Univariate correlations between subject characteristics and HS_{BMI} and HS_{BSA}.

Characteristics	Male ($n = 62$) HS_{BMI} r (p value)	Male ($n = 62$) HS_{BSA} r (p value)	Female ($n = 83$) HS_{BMI} r (p value)	Female ($n = 83$) HS_{BSA} r (p value)
Age (years)	-0.021 (0.869)	-0.004 (0.974)	0.001 (0.998)	-0.003 (0.978)
Anthropometry				
Lean tissue percentage (%)	0.568 (≤0.001)	0.459 (≤0.001)	0.286 (0.010)	0.194 (0.083)
Fat percentage (%)	-0.576 (≤0.001)	-0.441 (0.002)	-0.286 (0.010)	-0.171 (0.127)
Protein percentage (%)	0.57 (≤0.001)	0.467 (≤0.001)	0.285 (0.010)	0.190 (0.089)
Total water percentage (%)	0.577 (≤0.001)	0.468 (≤0.001)	0.287 (0.009)	0.204 (0.068)
Inorganic salt percentage (%)	0.494 (≤0.001)	0.383 (0.008)	0.241 (0.030)	0.138 (0.220)
Cardiorespiratory fitness				
AT (ml/kg·min)	0.158 (0.219)	0.188 (0.143)	0.062 (0.579)	0.123 (0.269)
VO_{2max} (ml/kg·min)	0.454 (≤0.001)	0.463 (≤0.001)	0.242 (0.028)	0.267 (0.015)
HR_{rest} (rpm)	-0.282 (0.026)	-0.332 (0.008)	-0.055 (0.619)	-0.024 (0.826)
HR_{AT} (rpm)	-0.232 (0.070)	-0.250 (0.050)	0.021 (0.850)	0.050 (0.657)
HR_{max} (rpm)	0.092 (0.478)	0.092 (0.475)	0.188 (0.089)	0.208 (0.059)
RER_{max}	0.181 (0.160)	0.139 (0.280)	0.125 (0.259)	0.081 (0.465)
VE_{max} (ml/min)	0.381 (0.002)	0.344 (0.006)	0.236 (0.032)	0.254 (0.020)
$Load_{max}$ (W)	0.342 (0.007)	0.340 (0.007)	0.201 (0.069)	0.191 (0.083)
$Psys_{max}$ (mmHg)	-0.068 (0.602)	-0.015 (0.908)	-0.254 (0.020)	-0.182 (0.100)
$Pdia_{max}$ (mmHg)	0.049 (0.703)	-0.005 (0.969)	0.100 (0.369)	0.131 (0.237)
MET_{max}	0.452 (≤0.001)	0.462 (≤0.001)	0.242 (0.027)	0.265 (0.016)
$\Delta VO_2/\Delta Load$	-0.147 (0.256)	-0.107 (0.406)	-0.049 (0.657)	-0.008 (0.943)
VE/VCO_2	0.243 (0.057)	0.147 (0.254)	0.175 (0.114)	0.205 (0.063)
OUES	0.005 (0.970)	0.081 (0.531)	0.079 (0.479)	-0.033 (0.769)
Life habit				
Smoking	0.081 (0.532)	-0.006 (0.966)	0.061 (0.584)	0.120 (0.281)
Exercise habits	-0.105 (0.418)	-0.101 (0.435)	0.125 (0.260)	0.166 (0.134)

SD: standard deviation; BMI: body mass index; BSA: body surface area; HS_{left}: handgrip strength of the left hand; HS_{right}: handgrip strength of the right hand; HS_{max}: maximum handgrip strength of the two hands; $HS_{average}$: average handgrip strength of both hands; HS_{BMI}: $HS_{average}$ adjusted for BMI; HS_{BSA}: $HS_{average}$ adjusted for BSA; AT: anaerobic threshold; VO_{2max}: max oxygen uptake; HR_{rest}: resting heart rate; HR_{AT}: heart rate at anaerobic threshold; HR_{max}: max heart rate; $Load_{max}$: max work load; RER_{max}: respiratory exchange ratio at max work load; VE_{max}: minute ventilation at max work load; $Psys_{max}$: systolic pressure at max work load; $Pdia_{max}$: diastolic pressure at max work load; MET_{max}: metabolic equivalent at max work load; $\Delta VO_2/\Delta Load$: oxygen required at each load; VE/VCO_2: the minute ventilation/carbon dioxide production slope; OUES: oxygen uptake efficiency slope. *r for categorical variables: Spearman's correlation coefficient; r for continuous variables: Pearson's correlation coefficient.

Anthropometric indicators also influence HS. In the current study, lean-tissue percentage, protein percentage, total water percentage, and inorganic salt percentage were positively correlated with HS_{BMI} and HS_{BSA}. Our findings are consistent with an earlier study, in which HS was positively correlated with lean tissue mass, lean tissue index, and serum albumin level in hemodialysis patients [29]. The possible mechanism for these associations may be that muscle mass forms the basis of strength, and protein, inorganic salt, and water establish the nutrition required for HS [30]. Conversely, it is known that a high body fat percentage is strongly correlated with cardiovascular and cerebrovascular diseases because of lipid-induced atherosclerosis [31]. In this study, body fat percentage was negatively associated with HS_{BMI} and HS_{BSA}; therefore, these associations may explain why a low level of HS is correlated with high cardiovascular risk [32]. Furthermore, in our study, we found, through multiple regression analysis, that almost all the associations between HS and body composition were covered by VO_{2max}, indicating that the relationship between HS and CRF was more stable than that between HS and other factors.

Previous studies have indicated a close association between HS and cardiovascular health and cardiac structure and function [33–35]. Beyer et al. found that a higher HS was associated with a higher left ventricular end-diastolic volume, higher left ventricular stroke volume, lower left ventricular mass, and lower left ventricular mass-to-volume ratio in UK adults [36]. Further, other studies have found that a lower HS may contribute to heart failure with a preserved ejection fraction through the pathways of the activation of systemic inflammation [37] and insulin resistance [38, 39]. Moreover, Zhang et al. reported that HS demonstrated a strong correlation with the six-minute walk test distance in older participants ($R = 0.549$, $p \leq 0.001$) [26], which is consistent with our findings. These relationships help establish the foundation of the association between HS and CRF.

Table 3: Multivariate regression analysis on the associations between subject characteristics and HS_{BMI} and HS_{BSA}.

Models	HS_{BMI} β (95% CI)	p value	HS_{BSA} β (95% CI)	p value
Male ($n = 62$)				
Age (years)	-0.005 (-0.018, 0.027)	0.686	-0.059 (0.419, 0.300)	0.740
VO2max (ml/kg·min)	0.016 (-0.002, 0.033)	0.073	0.215 (0.032, 0.398)	0.022
Lean-tissue percentage (%)	30.457 (-0.121, 70.035)	0.056	140.276 (-270.907, 560.459)	0.498
Fat percentage (%)	-20.712 (-50.349, -0.075)	0.044	-90.401 (-400.043, 210.240)	0.539
BMI (kg/m^2)	—	—	-0.200 (-0.767, 0.367)	0.480
BSA (m^2)	0.514 (-0.315, 10.342)	0.200	—	—
Female ($n = 83$)				
Age (years)	0.005 (-0.018, 0.027)	0.686	0.046 (-0.221, 0.312)	0.734
VO2max (ml/kg·min)	0.016 (0.004, 0.029)	0.011	0.173 (0.026, 0.321)	0.022
Lean-tissue percentage (%)	10.452 (-0.402, 30.306)	0.123	80.568 (-140.291, 310.427)	0.458
Fat percentage (%)	-10.805 (-30.712, 0.101)	0.063	-80.210 (-320.635, 160.216)	0.505
BMI (kg/m^2)	—	—	0.046 (-0.328, 0.420)	0.807
BSA (m^2)	0.475 (-0.044, 0.993)	0.072	—	—

β: effect size; CI: confidence interval; HS: maximum handgrip strength of the two hands; BMI: body mass index; BSA: body surface area; HS_{BMI}: $HS_{average}$ adjusted for BMI; HS_{BSA}: $HS_{average}$ adjusted for BSA; VO_{2max}: maximum oxygen uptake.

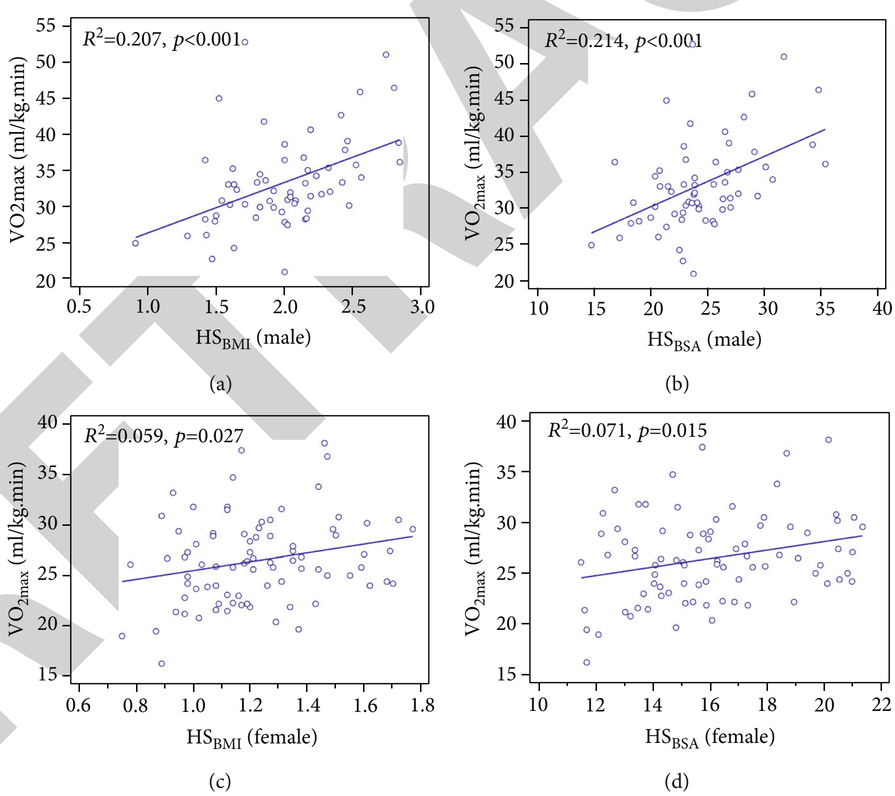

Figure 2: Linear regression between HS_{BMI} and HS_{BSA} with VO_{2max} in male and female young adults. (a) Linear regression between HS_{BMI} and VO_{2max} in male participants ($R^2 = 0.207$, $p < 0.001$). (b) Linear regression between HS_{BSA} and VO_{2max} in male participants ($R^2 = 0.214$, $p < 0.001$). (c) Linear regression between HS_{BMI} and VO_{2max} in female participants ($R^2 = 0.059$, $p = 0.027$). (d) Linear regression between HS_{BSA} and VO_{2max} in female participants ($R^2 = 0.071$, $p = 0.015$). BMI: body mass index; BSA: body surface area; HS_{BMI}: $HS_{average}$ adjusted for BMI; HS_{BSA}: $HS_{average}$ adjusted for BSA; VO_{2max}: maximum oxygen uptake.

Based on these findings, it may be promising to develop predictive models of VO_{2max} with nonexercise factors in frail populations in the future [40, 41].

The mechanism underlying the association between HS and CRF remains unclear. As reported in the literature, pyruvate dehydrogenase (PDH) might be one of the links. Love

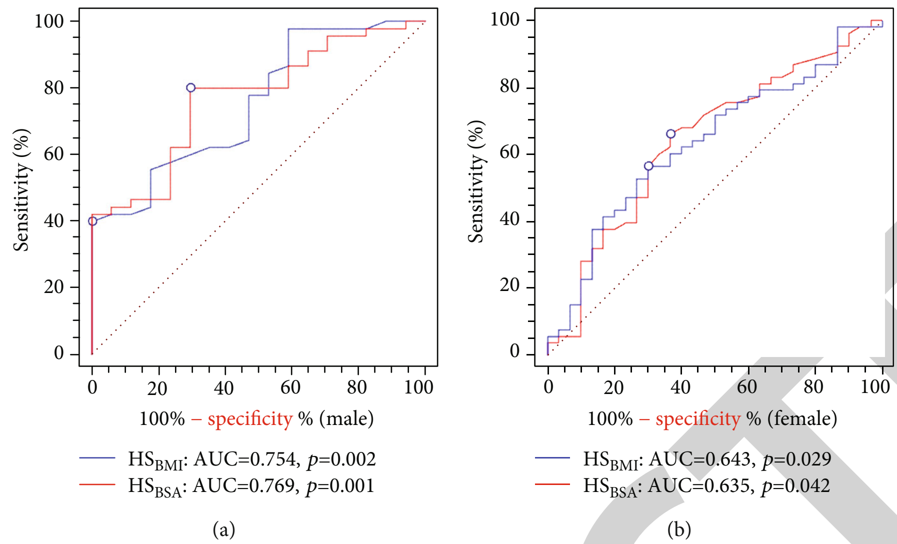

Figure 3: ROC analysis of the associations among HS_{BMI} and HS_{BSA} with VO_{2max} in male and female young adults. (a) The ROC curve between VO_{2max} and HS_{BMI} and HS_{BSA} in male participants. (b) The ROC curve between VO_{2max} and HS_{BMI} and HS_{BSA} in female participants. BMI: body mass index; BSA: body surface area; HS_{BMI}: $HS_{average}$ adjusted for BMI; HS_{BSA}: $HS_{average}$ adjusted for BSA; VO_{2max}: maximum oxygen uptake; AUC: area under curve.

et al. found that PDH phosphatase activity is associated with muscle aerobic capacity [42]. Muscle PDH phosphatase was found to be decreased in patients with low HS [43]. Additionally, aerobic training can increase PDH activity and improve maximal capacity to utilize carbohydrates in human skeletal muscle [44].

An interesting finding of this study was that the association between HS_{BMI}/HS_{BSA} and CRF was strong in young male adults but weak in young female adults. This may be because HS is strongly influenced by the heritability of sexually dimorphic traits [45], ranging between 50% and 65% for adult males, which is considerably lower for women (30%) [46]. Another reason may lie in the androgenic influences in the development of physical strength. Isen et al. found that, compared with girls, boys experience much more additive genetic effects of changes in HS during the period of adolescence (80% vs. 28%) [44]. Similarly, HS levels in men were much higher than that in women in our study. Meanwhile, because VO_{2max} level is the result of the combined effect of muscle strength and heart and lung function during extreme exercise, and because HS is strongly associated with overall muscle strength [1], the dominance of HS in men may result in a more significant relationship between HS and CRF than in women. These findings suggested that HS may be a good indicator of CRF in men but not necessarily in women.

The clinical significance of this study lies in the following. First, the close relationship between BMI- and BSA-adjusted HS and VO_{2max} may partly explain why HS is a risk factor of all-cause mortality and cardiovascular diseases. Second, the results provide evidence to support muscle strength training as a means to improve CRF. Third, HS, as a simple evaluation index, can moderately reflect the level of CRF and accordingly may act as a potential predictor of CRF levels in frail populations or communities where cardiopulmonary exercise testing is not possible.

There are some limitations to the present study. First, our research subjects were young healthy Chinese adults within a narrow age range limiting generalization to other populations. In future studies, subjects from different age groups should be included. Moreover, we excluded participants with congenital heart disease, a history of cardiac arrest, and muscular disorders. Therefore, the findings of this study cannot be generalized to people with these conditions. Finally, our sample size was small. Future studies with larger sample sizes are necessary to ensure generalizability of the findings.

5. Conclusions

Our results showed that HS_{BMI} and HS_{BSA} were correlated with various health-related indicators, including body composition factors (e.g., lean-tissue, protein, total water, and inorganic salt percentage) and CRF factors (e.g., VO_{2max}, VE_{max}, $Load_{max}$, and MET_{max}). HS_{BSA} was independently associated with VO_{2max} levels, especially in males. These associations may partly explain why HS is correlated with health risks. Therefore, we suggest that HS_{BMI} and HS_{BSA} could serve as indicators of physical health, and HS_{BSA} could be used to partially reflect CRF levels in healthy young adults. Larger studies are required to strengthen our conclusions and explore the application value of HS in varied populations.

Data Availability

All data used during the study are available from the corresponding author by request.

Conflicts of Interest

The authors declare no conflicts of interest.

Acknowledgments

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Supplementary Materials

Supplementary Material 1: STROBE checklist for cross-sectional study. Supplementary Material 2: ethical approval document. *(Supplementary Materials)*

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Research Article

Comparative Analysis of CNN and RNN for Voice Pathology Detection

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Diagnosis on the basis of a computerized acoustic examination may play an incredibly important role in early diagnosis and in monitoring and even improving effective pathological speech diagnostics. Various acoustic metrics test the health of the voice. The precision of these parameters also has to do with algorithms for the detection of speech noise. The idea is to detect the disease pathology from the voice. First, we apply the feature extraction on the SVD dataset. After the feature extraction, the system input goes into the 27 neuronal layer neural networks that are convolutional and recurrent neural network. We divided the dataset into training and testing, and after 10 k-fold validation, the reported accuracies of CNN and RNN are 87.11% and 86.52%, respectively. A 10-fold cross-validation is used to evaluate the performance of the classifier. On a Linux workstation with one NVidia Titan X GPU, program code was written in Python using the TensorFlow package.

1. Introduction

Speech is one of the basic human instincts and voices of the subsystem. Natural voice is the auditory result of pulmonary air bursts communicating with the larynx, which sets the adduction of true vocal folds and creates intermittent and/or aperiodic sounds. Sometimes, numerous abusive vocal patterns, typically referred to as vocal hyperfunction, result in speech disorders such as aphonia (complete lack of voice and/or dysphonia (partial loss of voice) [1]). Speech dysfunction is something that deviates "quality, pitch, loudness, and/or vocal flexibility" from voices of common age, gender, and social classes [2]. The consequence of nonmalignant speech disorders is not life-threatening, but the effects of untreated voice dysfunction may have a major impact on social, occupational, and personal aspects of communication [3]. Of the numerous vocal fold lesions, mass pathologies are particularly prevalent due to the phonotraumatic effect on vulnerable multilayer vocal folds, persistent tissue infection, and environmental stimuli frequently resulting in vocal nodules and vocal polyps [4]. In these conditions, the closing of the vocal fold is insufficient, and the production of the voice is not economical and perceptually hoarse. In the opposite, there are no vocal fold lesions in nonphonotraumatic voice disorders, such as muscle tension dysphonia and functional speech dysfunction, but vocal exhaustion, degraded voice quality, and increased laryngeal discomfort may be found. Multiparametric evaluation methodology is known to be suitable for voice assessment [1, 5]. Historically, a systematic approach is important and includes the following: patient interview, laryngeal examination via stroboscopy and/or laryngoscopy, simple aerodynamic assessment, auditory analysis by standardized psychoacoustic approaches, auditory analysis, and subjective speech assessment. In view of recent technical advances, voice scientists have been at the forefront of the creation of acoustic processing instruments to discern natural voice from those with aphonia and/or dysphonia. Structures for the expression recognition of voice disorders can be planned and built utilizing machine learning (ML) algorithms. Here, the voice data must be preprocessed and transformed into a series of features before an ML algorithm is used [6]. Experts could manually mark a collection of speech data in audio files as a safe or defective expression. Then, the original audio data in each file is split into short frames, and each frame is analyzed to remove the features from it. The set of features derived from all frames is called feedback for neural networks. The data collection is split into training and research sets by randomly choosing observations of both natural and pathological voices. The training set is used to build the machine learning algorithm, and the test set is used to validate the model. The precision of the designation is determined during the assessment process. This precision of classification shall be taken as a metric for determining the efficiency of the different Automatic Voice Disorder Detection (AVDD) programs [7].

There are a few gaps identified by Abid Syed et al. [8] in the area of voice disorder detection through Artificial Intelligence techniques like the lack of using unsupervised techniques by researchers in the detection of voice orders, the lack of the accuracy comparison, or the less work on Arabic Voice Pathology Database (AVPD) [9]. In this paper, we have used Saarbruecken Voice Database (SVD) [10] for the detection of voice order. The proposed paper is the continuation of the previous work of the authors [11] in which they first applied Support Vector Machine (SVM), Decision Tree, Naïve Bayes, and Ensemble, and then on the same set of features and disease, Syed et al. proposed comparative analysis of RNN and CNN. The aim of this paper is to design a system by first extracting features and then applying recurrent neural network (RNN) as a machine learning classifier to predict the accuracy of the system. Secondly, we will compare the results of RNN with convolutional neural network (CNN) and also try to increase the reported accuracy of the system using CNN because previously the highest reported accuracy using convolutional neural network is 80% in the meta-analysis [8]. In this paper, we will be using the SVD dataset which has voice recordings of vowel sounds of the patient with the different disease.

2. Related Work

Al-Nasheri et al. in [12–14] used SVM on SVD [10] to propose a system for voice disorder detection. In [12], Al-Nasheri et al. focus on creating a reliable and robust function extraction to identify and distinguish voice pathologies by analyzing various frequency bands using autocorrelation and entropy. Maximum peak values and their related lag values were derived from each frame of the spoken signal using autocorrelation as a function to identify and distinguish pathological samples. We have obtained the entropy for each frame of the speech signal after we normalized the values to be used as functions. These features were examined in different frequency bands to determine the contribution of each band to the identification and classification systems. Various examples of continuous vocal for both natural and abnormal voices were collected from three separate datasets in English, German, and Arabic. The help vector machine has been used as a classifier. The highest reported accuracy is 92% for SVD. In [13], the main purpose of this paper is to analyze Multidimensional Voice Software (MDPV) parameters in order to automatically identify and distinguish voice pathologies in different datasets and then to figure out which parameters behaved well in these two processes. The experimental findings reveal a clear difference in the efficiency of the MDPV parameters utilizing these databases. Highly rated parameters often varied from one database to the next. The best accuracy was achieved by utilizing the three top rated MDVP metrics organized according to the Fisher Discrimination Ratio of 99.98% for SVD. In this article [14]; we derived maximal peak values and their related lag values from each frame of the spoken signal using the correlation method as a feature to identify and identify pathology materials. These characteristics are studied in various frequency bands to see the contribution of each band to the identification and classification processes. The most contributive bands for both identification and designation are between the 1000 and 8000 Hz. The maximum rate of precision gained by utilizing cross-correlation is 99.809%, 90.979%, and 91.16% in the Massachusetts Eye and Ear Infirmary, Saarbruecken Speech Database (SVD), and the Arabic Voice Pathology Database, respectively. However, the maximum rate of precision acquired by utilizing cross-correlation was 99.255%, 98.941%, and 95.188%, respectively, in the three datasets. In [15, 16], Teixeira et al. proposed the system for voice detection keeping the same features in both of his publication but changing the classifiers. In [15], they used SVM with Jitter, shimmer, and HNR and the reported accuracy was 71%. In [16], they used MLP-ANN with Jitter, shimmer, and HNR and the reported accuracy was 100% but only for female voices. In [17], Fonseca et al. used SVM with SE, ZCRs, and SH and the reported accuracy was 95%.

Also, there is not much work done for voice pathology using a convolutional neural network. Only Guedes et al. [18] designed a system and reported an accuracy of 80%, and Zhang et al. [19] also use the DNN model which was machine learning where outcomes were missing. So after a detailed literature review, it was concluded that a novel system can be proposed using pitch, 13 MFCC, rolloff, ZCR, energy entropy, spectral flux, spectral centroid, and energy as features and RNN as a classifier

Table 1: Characteristics of SVD dataset.

Dataset	SVD		
	Language	Sampling frequency	Text
Characteristics	German	50 KHz	Vowel /a/ (1) Vowel /i/ (2) Vowel /u/ (3) Sentence

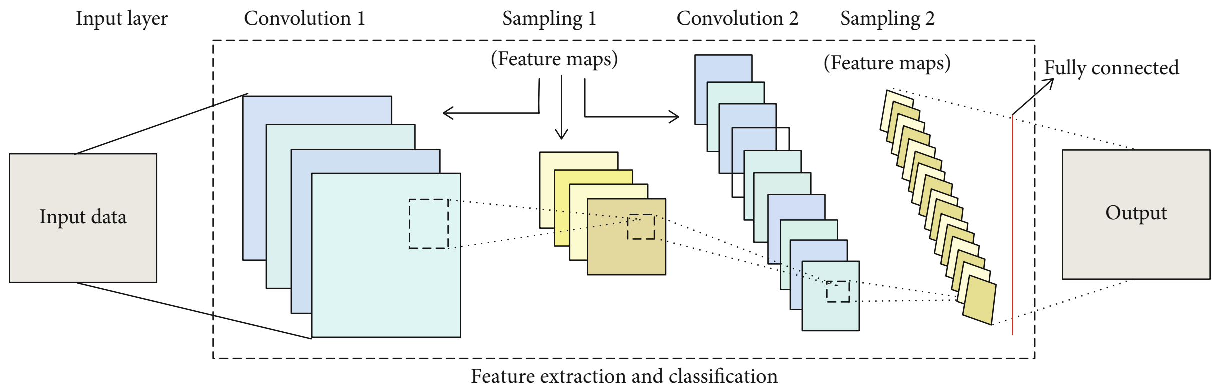

FIGURE 1: Architecture of CNN [22].

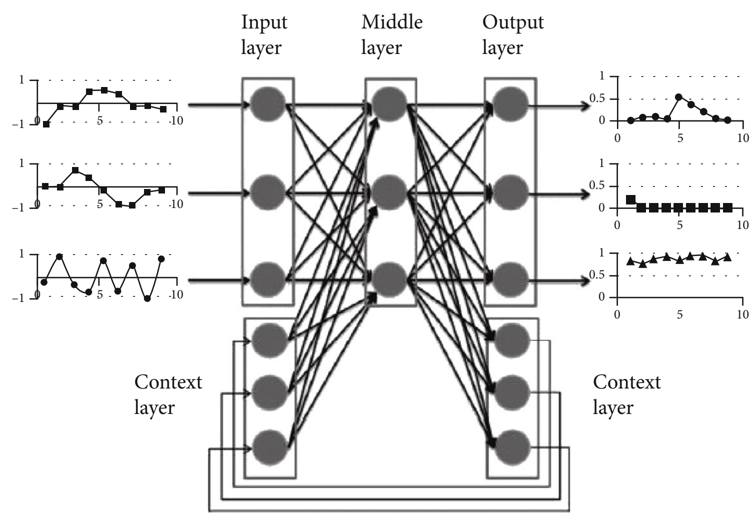

FIGURE 2: Architecture of LSTM-RNN [25].

to increase the accuracy and further using CNN to verified the results.

3. Materials and Method

3.1. Dataset. SVD stands for Saarbrücken Voice Database. In Table 1, the characteristics of SVD dataset are presented. Basically, SVD is a publically available database which is a collection of voice recordings by over 2000 people with over 72 voice pathological conditions: (1) vocal registration [I a, u] produced at standard, high, and low pitches, in which the truth was recorded in a recording session;(2) vocal documentation of increasing pitch [I a, u]; and (3) recording of the phrase "Good morning, how do you like it?" ("How are you, good morning?"). The voice signal and the EGG signal were stored in individual files for the specified components [11]. The database has text file including all relevant information about the dataset. Those characteristics make it a good choice for experimenters to use. All recorded SVD voices were sampled with a resolution of 16-bit at 50 kHz. There are some recording sessions where not all vowels are included in each version, depending on the quality of their recording. The "Saarbruecken Voice Server" is available via this web interface. It contains multiple internet pages which are used to choose parameters for the database application, to play directly and record and pick the recording session files which are to be exported after choosing the desired parameter from the SVD database [12]. From the SVD database, the disease we have selected are "Balbuties," "Dysphonie," "Frontolaterale Teilresektion," "Funktionelle Dysphonie," "Vox senilis," "Zentral-laryngaleBewegungsstörung," "ReinkeÖdem," "Stimmlippenpolyp," "Stimmlippenkarzinom," "SpasmodischeDysphonie," "Psychogene Dysphonie," and "Leukoplakie" [11]. The diseases were solely selected on the basis of common diagnosis of voice disorders.

3.2. Feature. The features that are extracted from samples to perform this study are 13 MFCC features, pitch, rolloff, ZCR, energy entropy, spectral flux, spectral centroid, and energy. Syed et al. in their previous work [11] add seven more features, i.e., pitch, rolloff, ZCR, energy entropy, spectral flux, spectral centroid, and energy, to produce more enhanced voice sample for processing.

3.2.1. Mel-Frequency Cepstral Coefficients (MFCC). In 1980, MFCC was suggested by Davis and Mermelstein for the most widely used speech recognition feature [20]. Primarily, the exhaustion method for the MFCC function involves

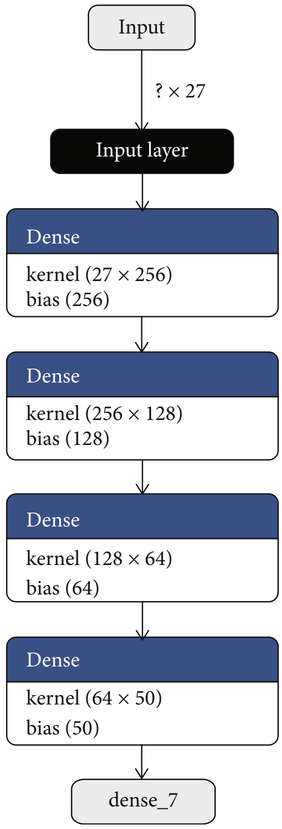

Figure 3: Proposed in-layer model of CNN.

windowing the signal, applying the DFT, acquiring the magnitude protocol, and then shaming the values and a Mel rank on scale, then applying a reverse DCT. The cepstral coefficients normally include only details from a specific frame and are considered static attributes. The machine first and second derivatives of cepstral coefficients have the additional information on time dynamics of the signal [21].

$$\hat{y}_t[j] = \frac{y_t[j] - \mu(y[j])}{\sigma(y[j])}. \quad (1)$$

3.2.2. Pitch. The pitch corresponds to the level at which during a noise voicing cord vibrates. Standard approaches such as the autocorrelation system and the method of average magnitude differential at max, resulting in half and double-half defects, are vulnerable to mutation during the removal of tonnes. By distinguishing the acoustic pulse cepstrum from the vocal tract cepstrum, the cepstrum system may approximate the pitch. At the cost of complex measurements, it has high detection performance for regular voice signal [19].

3.3. Neural Networks

3.3.1. CNN Architecture. The CNN has several hierarchy levels composed of routing layers and grouping layers, which are defined by a broad variety of charts. In general, CNN begins with a convolutionary layer that accepts input level data. For convolutionary operations with few filter maps of the same dimension, the convolution layer is liable. In addition, the output from this layer is transferred to the sample layer that decreases the scale of the next layers. CNN is locally related to a vast variety of deep learning techniques. These networks are then implemented on the basis of GPU architecture on a number of hundred cores. The role maps will be allocated on the basis of the previous layer knowledge blocks [22]. It depends on the dimensions of the maps. However, each thread is bound to a single neuron by means of a single block of many threads. Similarly, neuron convolution, induction, and summation are carried out over the remainder of the method. Finally, a global memory stores the performance of the above processes. A backward and propagation model is adopted for the efficient processing of results. However, a single spread would not yield positive outcomes, so pulling or moving operations contribute to parallel spread.

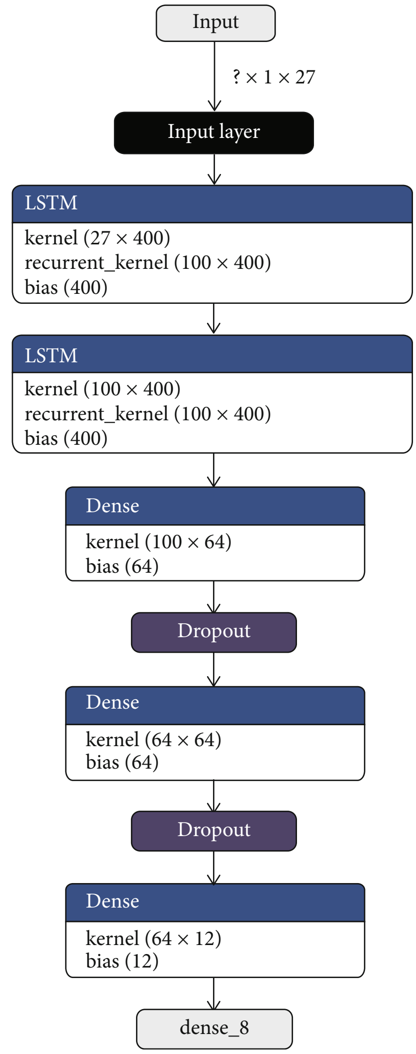

Figure 4: Proposed in-layer model of LSTM-RNN.

Table 2: Accuracy of RNN and CNN at 10-fold verification.

Algorithm	Validation	Accuracy
CNN	10-fold	87.11%
LSTM-RNN	10-fold	86.52%

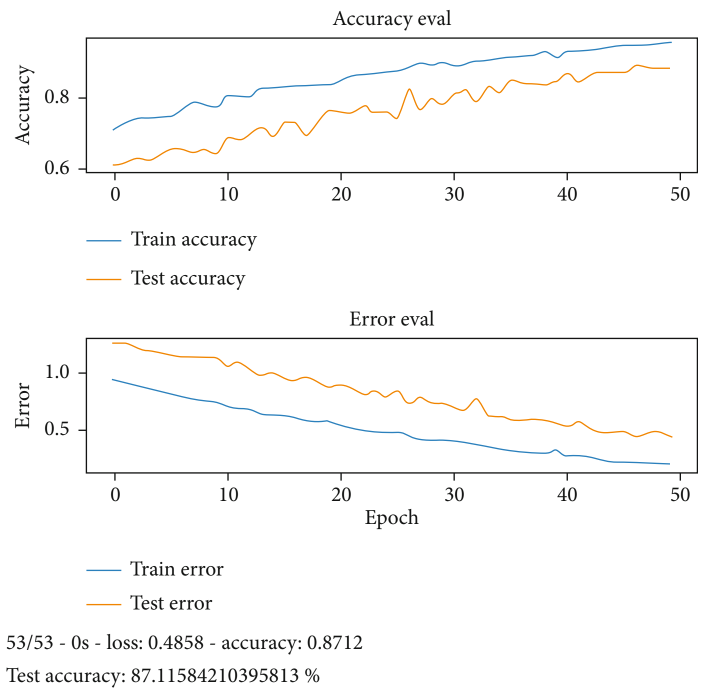

Figure 5: Accuracy and error evaluation of CNN in training and testing phase.

In addition, the neurons of a single layer interact with a separate number of neurons, influencing the boundary effects [23].

In Figure 1, the general architecture of CNN is explaining the work of this deep learning neural network. A deep learning algorithm includes input preprocessing, deep learning model training, storage of the learned model, and the last phase of the model implementation. In these phases, the most computational (or data intensive activity is to train the deep learning algorithms (defining and running). The model is provided some input through a neural network that produces some output at the specified step (also called forward transmission). The weights are changed if the performance is inappropriate or inaccurate (backward pass). This could be like a basic matrix multiplication, where input (first matrix row) for such unique output objects is multiplied by weight (second matrix column). Serial systems (CPU-based) are typically not feasible for higher order matrices (large inputs and weighs). Fortunately, GPU delivers much superior options than conventional single or cluster CPU systems [24] of graphic processing units for general purposes.

3.3.2. RNN Architecture. Long short-Term Memory (LSTM) is a special architecture of the recurring neural network (RNN) constructed more reliably than traditional RNNs and is designed to model temporal sequences and their long-range dependencies. Recently, we have shown that LSTM-RNN is more powerful than DNNs and standard acoustic modelling, taking into account models of moderate size trained on a single computer. We illustrate the potential to achieve the newest technology in speech recognition with a two-layer deep LSTM-RNN with a linear repeating projection layer. In Figure 2, the LSTM-RNN general architecture represents the working flow of the model. This design uses

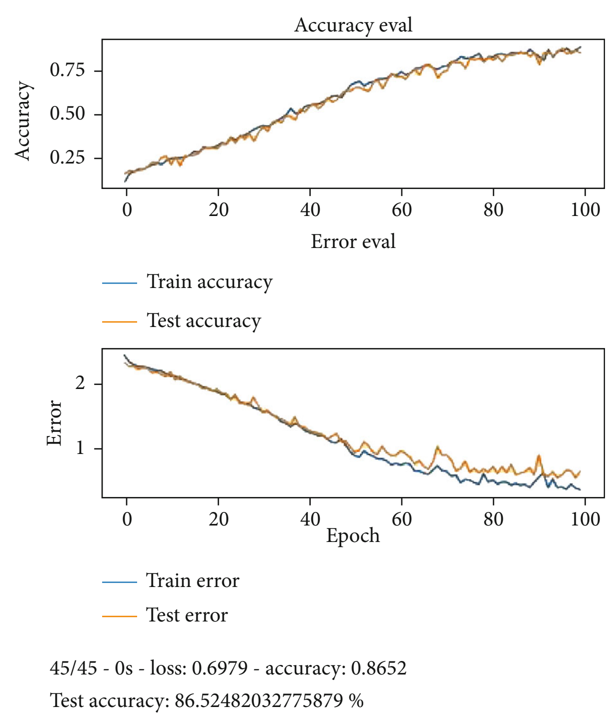

Figure 6: Accuracy and error evaluation of RNN in training and testing phase.

the model parameters more efficiently than other parameters, converges fast, and outperforms a deep neural network feed with a higher magnitude order. Speaking is a dynamic signal with time fluctuations with complex associations on a number of timescales. Recurring neural networks (RNs) have cyclic ties that render them more efficient than feedforward neural networks in modelling certain sequence data. RNNs

```
confusion_matrix#CNN

array([[100,   2,   4,   0,   0,   0,   5,   0,   0,   0,   2,   4],
       [  2, 141,   0,   0,   0,  11,   1,   0,   0,   5,   0,   0],
       [  0,   0, 165,   0,   0,   0,   0,   0,   0,   0,   0,   0],
       [  1,   9,   0, 126,   0,  12,   3,   1,   0,   3,   3,   0],
       [  0,   0,   6,   3,  70,   0,   4,   0,   0,   2,   0,   0],
       [  0,   0,   0,   0,   0, 180,   0,   0,   5,   4,   0,   0],
       [  9,   0,   0,   0,   0,   0, 168,   0,   0,   7,   4,   0],
       [  0,   0,   0,   0,   0,   2,   0, 157,   2,   6,   0,   0],
       [  3,   0,   3,   0,   0,   0,   0,   0,  99,   0,   0,   0],
       [  0,   3,   0,   0,   0,   3,   5,   0,   0, 148,   0,   0],
       [  0,   0,   7,   9,   1,   0,   6,   8,   4,   7,  88,   0],
       [  0,   0,   0,   2,   0,   3,   6,   0,   0,  10,   0,  48]])
```

Figure 7: Confusion matrix of CNN.

have been very effective in sequence marking and prediction activities such as handwriting and language detection [25].

The key distinction between CNN and RNN is the capacity to process transient or sequentially produced knowledge for example, in a phrase. In comparison, convolutionary neural networks and repetitive neural networks are used for entirely different uses, and the neural network architectures themselves vary to match these different cases of use. In order to convert results, CNNs use filter in convolution layers. In comparison, RNNs reuse activation functions from other sequential data points to build the following sequence production. Although this is an often discussed query, the distinction between CNN and RNN becomes apparent as you analyze the nature of neural networks and realize what they are used for.

4. Experiments and Evaluation

4.1. Proposed Model Layer of CNN and RNN. At the beginning of any study, the data needs cleaning, organized and error free. For any dataset loaded into the Python Pandas DataFrame, it is almost always necessary to remove different rows and columns in order to get the correct data collection for your particular study or visualization. In python for a simplified data model, we have used the command of "DataFrame.drop ()" which drop all the unnecessary columns and frames and give the simplified version of the speech samples. By defining label names and related axes or by explicitly specifying index or column names, you may exclude rows or columns. Labels from various levels may be eliminated by using a multiindex by defining the rank [26].

Similarly, for preprocessing, we have import "train_test_split" from "sklearn.model_selection" and "LabelEncoder" and "StandardScaler" from "sklear.preprocessing" The train-test split protocol is used to approximate the accuracy of machine learning algorithms as they are used to make decisions about data not used to train the model. It is a short and simple process to run, the results of which enable you to compare the output of machine learning algorithms with your predictive modeling problem. While it is easy to use and interpret, there are occasions where the protocol may not be utilized, such as when you have a limited dataset and cases when extra tuning is needed, such as when it is used for classification and when the dataset is not balanced. The technique entails the acquisition of a dataset and the division into two subsets. The first subset is used to match the model and is called the testing dataset. The second subset is not used to train the model; however, the dataset input element is given to the computer; then the predictions are rendered and compared to the predicted values. The second dataset is referred to the test dataset [27]. The 2000 selected recordings from the dataset were randomly divided into 80% and 20%. The 80% was included for training, and 20% was included was testing.

Figures 3 and 4 demonstrate the internal layering diagram of the proposed model of CNN and RNN. In proposed methodology, both CNN and RNN are 27 neuronal layer architectures with different bias values.

4.2. Results. The idea is to detect the disease pathology from the voice. First, we apply the feature extraction on the SVD dataset. In proposed methodology, the features that we have extracted are 13 MFCC features, pitch, Rolloff, ZCR, energy entropy, spectral flux, spectral centroid, and energy. After the feature extraction, the system input goes into the 27 neuronal layer neural networks that are convolutional and recurrent neural network. We divided the dataset into training and testing, and after 10 k-fold validation, the reported accuracies of CNN and RNN in Table 2 are 87.11% and 86.52%, respectively. There were 7 residual layers of the convoluted kernels of 27 residual blocks. Dropout with a frequency of 0.5 was used to maintain L2 normalization. For success assessment, 10-fold cross-validation has been used. Software code has been published on a workstation with one NVidia Titan X GPU using the TensorFlow plugin in python. Figures 5 and 6 represent the detailed accuracy and error evaluation with the lines drawn for training testing phase. The graph lines are joined in RNN evaluations which shows that the error margin is very minor, but in CNN evaluation, there are differences between the lines which show the probability of

```
confusion_matrix#RNN

array([[ 83,   0,   0,   1,   0,   0,   3,   1,   0,   2,   0,   0],
       [  1, 117,   0,  12,   0,   2,   0,   0,   3,   5,   2,   0],
       [  0,   0, 134,   0,   0,   0,   0,   5,   7,   0,   3,   0],
       [  0,   2,   0, 119,   0,   1,   3,   0,   0,   2,   5,   1],
       [  0,   0,   0,   4,  67,   0,   0,   0,   3,   0,   0,   1],
       [  0,   0,   0,   4,   0, 117,   1,   0,   0,   5,   0,   2],
       [  0,   2,   0,   1,   1,   0, 107,   0,   2,  12,   5,   2],
       [  0,   0,   0,   0,   0,   0,   0, 137,   0,  14,   3,   0],
       [  0,   0,   0,   0,   0,   0,   0,   2,  95,   4,   0,   0],
       [  0,   3,   0,   0,   3,   0,   0,   0,   2, 130,   0,   0],
       [  0,   3,   0,   0,   0,   1,   0,   0,   1,  10,  96,   4],
       [  0,   0,   0,   5,   0,   0,   0,   0,   0,   2,   0,  45]])
```

Figure 8: Confusion matrix of LSTM-RNN.

error margin in the proposed CNN algorithm which is higher than the RNN. Figures 7 and 8 represent the confusion matrix with the value that shows the number of correct diagnosis of the system.

5. Limitation

We understand that our neural network classifiers always have to attain optimal results. The exact measures, however, are superior to or close to other reported NLP reports. For example, while 10 of the 1000 test cases in the CNN model were a mistake, the classification errors in neural networks are very challenging to explore, since they are mostly "black boxes". A lack of direct mention of the primary cause of error was PE and limited documentation because of shortage or absence of insufficient quality of the image; inference based on the context was required instead. The model focused on RNN correctly forecasts the groups and located the most relevant sentences of the papers, but the model's inference is still difficult to generalize. We have seen just one case of a positive/negative PE classification, where CNN correctly forecasts it to be positive, but RNN forecasts it to be negative. It was not therefore evident how CNN might correctly predict this case on the basis of the heat map produced. Therefore, all of these mistakes need a subtle logic, which can restrict the design of our models, in addition to training limits raised by the scale of our data sets.

6. Conclusion

The amount of work done in this field concluded that clinical diagnosis voice disorders through machine learning algorithms have been the area of interest for most researchers. Hence, after applying the proposed methodology, we are able to increase the accuracy of the convolutional neural network which is 87.11% which is increased from the accuracy reported in the literature review. Comparatively, the accuracy of the recurrent neural network also closes to CNN and the predicted outcomes were almost the same. For future work, continuing to work with a neural network in the SVD dataset for the detection of voice pathology can report better accuracies.

Data Availability

The data base used for this particular study is an open source data available at this link http://www.stimmdatenbank.coli.uni-saarland.de/help_en.php4.

Conflicts of Interest

The authors declared that they have no competing interests.

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Review Article

Application Prospect of Artificial Intelligence in Rehabilitation and Management of Myasthenia Gravis

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Myasthenia gravis (MG) is a chronic autoimmune disease of the nervous system, which is still incurable. In recent years, with the progress of immunosuppressive and supportive treatment, the therapeutic effect of MG in the acute stage is satisfactory, and the mortality rate has been greatly reduced. However, there is still no consensus on how to conduct long-term management of stable MG, such as guiding patients to identify relapses, practice exercise, return to work and school, etc. In the international consensus guidance for management of myasthenia gravis published by the Myasthenia Gravis Foundation of America (MGFA) in 2020, for the first time, "the role of physical training/exercise in MG" was identified as the topic of discussion. Finally, due to a lack of high-quality evidence on physical training/exercise in patients with MG, the topic was excluded after the literature review. Therefore, this paper reviewed the current status of MG rehabilitation research and the difficulties faced by stable MG patients in self-management. It is suggested that we should take advantage of artificial intelligence (AI) and leverage it to develop the data-driven decision support platforms for MG management which can be used for adverse event monitoring, disease education, chronic management, and a wide variety of data collection and analysis.

1. Introduction

Myasthenia gravis (MG) is a chronic autoimmune disease affecting the postsynaptic membrane at the neuromuscular junction thereby obstructing nerve impulse transmission [1, 2]. The prevalence rate (PR) of MG is 15 to 179 cases per million, estimated pooled PR is 77.7; and the incidence rate (IR) is 1.7 to 21.3 cases per million person-years, estimated pooled IR is 5.3 [3]. MG treatment traditionally includes the symptomatic treatment by acetylcholinesterase inhibitors, thymectomy, steroids and/or nonsteroidal immunosuppressive therapy, intravenous immunoglobulin (IVIg), or plasmapheresis. Advancements in therapeutics have significantly reduced MG-associated mortality [4, 5]. However, the disease still affects most patients' daily functional activities and reduces their quality of life [6–9]. Since it is difficult for patients with MG to achieve complete stable response (CSR), the current international consensus has proposed minimum performance state (MMS) or better as the treatment goal of MG [10]. Therefore, the chronic management of MG includes complex pharmacotherapy and lifestyle-related activities, which must be optimized to improve the quality of life in patients and enable as many patients as possible to achieve MMS or better treatment goals. In the past few years, more and more AI-based software and hardware have been developed for the management and clinical research of chronic diseases. In this review, we introduce the successful experience of AI in several chronic disease management and discuss the possible application of AI in the rehabilitation and management of MG in the future.

2. Current Status and Dilemma of Rehabilitation and Management in MG

For a long time, physicians have paid more attention to the treatment of acute symptoms in MG; however, the potentially prolonged course of the disease remains neglected. In many MG patients, even if symptoms are improved by standardized treatment after onset, they will soon be plagued again by disease recurrence or drug-related adverse events.

Here are several common reasons: (1) relapse as a consequence of early withdrawal of medication, undertaken due to resolution of symptoms; (2) adverse events caused by failure to regularly monitor the safety of medication; (3) other chronic diseases caused by long-term use of glucocorticoids and immunosuppressive drugs; and (4) relapse of MG for unknown causes. With the prolongation and fluctuation of the disease, MG patients are often puzzled over the period of their treatment. “How much and how long should I take my medicine? What should I pay attention to in my daily life? Can I do physical exercise? When can I go to work? Why is my sleep getting worse?” Even in the recently published consensus guidance for management [11], the expert group did not give clear recommendations for the management of stable MG patients. Some studies have shown that most MG patients are often restricted when engaging in social activities, such as entertainment or work. Patients present with depression, anxiety, social reclusiveness, and frustration to a certain extent, arising from their MG [12–14]. Therefore, treatment strategies should also include the long-term management of MG and aim towards an improved quality of life and mental health [15].

The preventive benefits of physical exercise in various chronic diseases such as stroke, heart diseases, and cancer are well known, and its role in promoting positive psychological effects is beginning to be widely accepted at the same time [16–18]. Physical exercise has even been compared to drug therapy and has been therefore recommended as part of the management of many chronic diseases.

Traditionally, it was believed that physical training/exercise exacerbated symptoms for MG patients. However, the current general opinion supports that MG patients can benefit from physical exercise, which the evidences coming from a small number of physical exercise clinical trials. In a stratified study by Rahbek et al. [19], patients were assigned randomly to either the aerobic training (AT) group or the progressive resistance training (RT) group intervention over 8 weeks. Primary results showed that MG patients were well tolerated to both types of physical intervention within a specified time period (i.e., 8 weeks). Secondary results showed that muscle strength and functional capacity improved in the RT group, compared with no change in the AT group. A prospective study, by Westerberg et al. [20], supervised AT and RT twice weekly for 12 weeks with MG patients. While the study did not report increased muscle strength but the patient performed significantly better on the physical fitness tests such as the 6-min walk test and 30-second-sit-to-stand test. Another study incorporating respiratory training on stable MG patients for a period of 8 weeks used a case-control approach by randomly dividing patients into cohorts. The patients were trained for diaphragmatic breathing and pursed lips breathing. Compared to the controls and to the individual baseline values, patients had improved respiratory muscle endurance, maximum inspiratory and expiratory pressures, and thoracic mobility [21].

In the international consensus guidance for management of myasthenia gravis: 2020 update [11], for the first time, “the role of physical training/exercise in MG” was identified as the topic of discussion, which shows that more and more experts have begun to pay attention to the exercise rehabilitation and chronic management of MG patients. However, the low quality of evidence with respect to physical training/exercise and its significance in the management of chronic MG led to its noninclusion as an informing recommendation. So, what are the factors that limit the design and completion of high-quality clinical trials on physical exercise in MG? We summarized the following reasons: (1) it is difficult to recruit subjects. The first step in MG clinical trial is to select subjects based on strict and well-defined criteria for inclusion and exclusion, such as age, course of disease, subtype, severity, concomitant diseases, and received interventions. In addition, the low incidence rate of MG further increases the difficulty of recruitment. Each trial will be recruited within a certain time window. Enrolling enough patients within the specified time is a necessary condition for the success of a trial; (2) in order to ensure the real and effective exercise data, trainings need supervision, which limit the activity scope and activity time of subjects and reduce their compliance; (3) prolonged interventions will introduce more influence factors, making prospective study designs difficult; (4) selection criteria for control group is unclear; (5) double-blind trials cannot be designed; (6) absence of clarity or consensus with respect to standard outcomes in MG is missing.

3. Application of AI in the Management of Chronic Diseases

3.1. Artificial Intelligence Techniques. The basic idea of artificial intelligence (AI) is to simulate human thinking through a computer, that is, the process of perceiving the world, learning constantly, and making decisions. AI is an emerging field in computer sciences which involve human independent application of specifically designed computer algorithms. AI approaches fall into three categories [22]: (1) exploration and discovery of knowledge, this is also known as knowledge discovery in databases (KDD). KDD is primarily used for identifying information validity. It segregates information as relevant/useful and nonrelevant/nonuseful. One of the important steps towards knowledge discovery is data mining. Data mining technology mainly includes decision tree, neural network, regression, association rule, clustering, and Bayesian classifier; (2) learning from knowledge, the method permits learning from the acquired knowledge. Computers can learn on their own without any assistance or intervention from humans. The method is aimed to enable better decision-making and more accurate predictions about future conditions; (3) reasoning from knowledge is the third method. In this method, the existing knowledge becomes the starting point, and using logical techniques, such as deduction and induction, a hypothesis is proved or disproved and helps derive conclusions. For instance, an intelligent medical diagnosis system can diagnose based on the clinical and pathological presentation of the disease, using the knowledge in the databases and the control strategies.

3.2. Emerging Application of AI in Medicine. AI was first used in medicine in the 1970s, but the development in the field of medicine has been slow in the following decades. Until the last few years, with the development of information and communication technologies, things have changed. First, the rapid development of software and hardware technology makes it possible to obtain widely available medical data. The popularity of electronic health records (EHR) and the emergence of sensors and wearable devices are promoting the evolution of medical data to digital form. The massive medical data obtained can be processed in real time and efficiently by using big data analysis technology, such as machine learning, deep learning, and data mining. Secondly, the real-time transmission and sharing of information are realized through the Internet. 5G communication technology is about to promote the transformation of mobile Internet to the Internet of everything. The progress and combination of these technologies are driving new developments in the field of medical technology. At present, AI is widely used in health technology. They are utilized at every stage of disease management, including disease screening, [23, 24], disease diagnosis [25–28], prognosis estimation [29, 30], decision support [31], and therapeutic recommendation [32]. Recently, AI attracted considerable interest for its advantages in health and chronic disease management [33, 34].

3.3. Examples of AI Applications in Chronic Disease Management. The full name of chronic diseases is chronic noncommunicable diseases (NCDs). The common chronic diseases mainly include cancer, diabetes, hypertension, obesity, chronic respiratory diseases, chronic kidney diseases, autoimmune diseases, cardiovascular and cerebrovascular diseases, and neurodegenerative diseases [35]. Globally, chronic diseases are known to affect nearly a quarter of the adult population and are known to have a huge negative socioeconomic impact [34]. In the following, we will introduce some examples of AI application in chronic disease management and related research.

Chronic disease management requires patient monitoring advice and status assessment. This is one of the application areas to explore AI methods in combination with other mobile computing and sensor technologies, which is expected to create and provide better services for chronic disease management. For instance, in diabetes, AI methods are used for blood sugar monitoring, lifestyle recommendations, and self-management. Exploration of a computerized decision support system (DSS) for diabetes has been undertaken. These computer applications monitor disease outcomes by recording information about diet, exercise, drug use, and blood glucose levels [36, 37]. The utility of such digital technology can also be seen in the management of chronic lung conditions. Res-App is used for monitoring patient breathing through the phone microphone providing an evaluation for several lung diseases, such as asthma, pneumonia, lower respiratory tract disease, croup, and bronchiolitis [38]. Altogether, a combination of sensor-based and computerized technologies either in form of wearable devices or an electronic health record database has helped improve the management of some chronic diseases through the integration of geospatial and clinical data [39, 40].

In cancer research, AI is widely used to evaluate the degree of tumor invasion, predict the course of the disease and prognosis, and give the advice on treatment, especially provides a strong analytical support for the study of breast cancer [41], hepatocellular carcinoma [42], and nasopharyngeal carcinoma [43]. Recently, the US Food and Drug Administration (FDA) has licensed several AI systems to develop testing devices for early diagnosis of cancer [44].

Through the AI algorithm, dozens or even hundreds of groups of data can be analyzed in detail to reveal the inherent laws of diseases and find out the associated factors of the occurrence, development, treatment, and prognosis of some chronic diseases, which is beyond the ability of human beings themselves. A prospective cohort study of 500,000 subjects was completed in the UK. Each subject provided data including biological measurements, lifestyle indicators, biomarkers in blood and urine, and brain imaging information. The researchers also collected genome-wide gene data of all subjects, aiming to look for genetic associations associated with chronic diseases and their characteristics by using big data analysis [45]. Also, in an eight-year study, 109 subjects at high risk of type 2 diabetes received each quarter a measuring and sampling, including the clinical signs measurement, group analysis (genome, immunome, transcriptome, proteome, metabolome, and microbiome), and wearable equipment measurement. Finally, the analysis revealed 67 clinically actionable health discoveries and developed a predictive model for insulin resistance [46]. Without AI-based machine learning algorithms, such huge and complex data analysis was unimaginable in the past. Machine learning is also widely used in the field of nutrition to develop personalized diet management and prevent diet-related diseases [47].

4. Application Prospect of AI in Rehabilitation and Management of MG

4.1. Establish Monitoring System of Medication Safety and Adverse Events. Long-term treatment with immunosuppressive drugs is essential for most MG patients, and glucocorticoids in particular are irreplaceable. Oral prednisone is recognized as the first-line immunotherapy for MG, but the cumulative exposure dose of prednisone is associated with an increased risk of adverse reactions, including obesity, osteoporosis, abnormal glucose metabolism, and infection. Nonsteroidal immunosuppressants (such as azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, cyclophosphamide, and methotrexate) are recommended to be used in combination with glucocorticoids or alone for long-term (even lifelong) treatment [10, 11]. Treatment-related adverse event (AE) arising due to immunosuppressive therapy in the initial months should be strictly monitored, such as leukopenia, thrombocytopenia, hepatic dysfunction (particularly with azathioprine treatment), or renal dysfunction (more common with cyclosporine treatment) [48], which has often been neglected in the past. According to statistics, over 90% of AE or serious adverse event (SAE) are not reported in spontaneous reporting systems [49]. Through the digital management platform, an effective utilization of AI technology could send reminders of drug safety monitoring to patients regularly, process the acquired monitoring data in real time, warn patients and doctors of abnormal data, and realize remote monitoring of treatment. Remote management of MG may work to be of much use for the aged patients with travelling difficulties, or in geographically challenged territories, or in times when healthcare facilities are not easily accessible such as pandemic periods.

4.2. Conduct Personal Life Guidance and Disease-Related Education. Patients using steroids should be supplemented with calcium and vitamin D and should be given with bisphosphonate therapy appropriately. At the same time, a generally healthy diet should be advised for all patients. It is worth noting that methotrexate and cyclophosphamide should be avoided in women of childbearing age because of their teratogenic effects. Some drugs associated with MG deterioration need to be used with caution and only upon suitable prescriptions from the doctors [48]. The similar notes and related knowledge, including diet, lifestyle, sleep, stress, and exercise habits, should be easily accessible to MG patients at any time on the management platform, and relevant safety warnings should be made according to the data generated by the patients. The management platform should be set up with an education section and constantly updated to improve the patient's self-management skills. It is worth learning from the application of AI in the individualized management of diabetes patients, including AI assisting diabetic patients to make scientific diet plan, carry out appropriate physical exercise, monitor the occurrence and development of common complications, and even provide technical support for patients in blood glucose monitoring and insulin use [21, 32].

4.3. Develop a Social Platform for Mutual Benefit between Doctors and Patients. The digital management platform itself also has the social function of communication. The growing partnership and cooperation are the foundation of development. Doctors can recruit the clinical trial subjects, spread knowledge, and demonstrate professionalism through the platform; patients can gain knowledge; understand condition; develop their own social network; read news; and share blogs, photos, and videos.

4.4. Participate in the Research Data of MG Rehabilitation and Management. Although, as mentioned above, clinical research on MG rehabilitation is currently facing difficulties, and there seems to be an opportunity to break through this bottleneck with the continuous maturity of AI technology and the development of information and communication technologies. First, AI will be applied to subject recruitment. After the establishment of MG management platform, patient information will be stored and accumulated and, gradually, developed into a valuable clinical resource database. When a study needs to recruit subjects, AI can preliminarily screen and match qualified subjects according to the inclusion and exclusion criteria and, then, recommend candidate subjects to doctors and provide their contact information so as to improve the efficiency of recruitment, expand recruitment coverage, and influence and achieve the best match. Instead of making regular trips to the hospital to participate in clinical trials, patients will receive remote monitoring, treatment, and life guidance. This AI-based clinical trial matching system has been successfully tested at the Mayo Clinic [50]. AI will provide more benefits to the subjects and improve their compliance. For example, AI can provide doctors with automatic, continuous, and real-time monitoring information from subjects through the management platform, so that subjects can get more attention from doctors.

In addition, wearable sensors and video surveillance can be used to automatically and continuously collect patient data, which is becoming increasingly available through the introduction of App-based and sensor-based exercise and therapy management systems [51]. For example, a trial of telerehabilitation after stroke [52] and a study in Parkinson's disease [53], both used data from sensors that measured body movement. For MG, we propose to establish a digital management platform that allows patients in consultation with physiotherapists to allocate patient-specific physical regimen to either the patient or the caregiver. The mobile technology may also allow the collection of adherence data. This real-time collection of data enables to minimized loss of data and ensures volume, variety, and velocity of data collection. The three V's of big data era will allow trend detection and correlations through the application of big data analytic tools. In the future, when enough available data are obtained, big data technologies will use all types of full data (not sample data) to draw reliable statistical conclusions, instead of extrapolating the real world around a small sample of data.

5. Conclusion

MG is an incurable disease. Rehabilitation and individualized patient management are essential components of MG lifetime therapy. In the future, drawing on the successful experience of AI in other chronic disease management, it is an unstoppable trend to develop MG digital management platform with functions such as education, management, social contact, and access to research data.

Abbreviations

AE: adverse event
AI: artificial intelligence
CSR: complete stable response
EHR: electronic health records
FDA: Food and Drug Administration
IVIg: intravenous immunoglobulin
MG: myasthenia gravis
MGFA: Myasthenia Gravis Foundation of America
MMS: minimum performance state
NCDs: noncommunicable diseases
SAE: serious adverse event.

Data Availability

This article has no additional data.

Conflicts of Interest

The authors declare that they have no conflicts of interests.

Acknowledgments

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Retraction

Retracted: Urine Albumin/Creatinine Ratio and Microvascular Disease in Elderly Hypertensive Patients without Comorbidities

BioMed Research International

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This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope

(2) Discrepancies in the description of the research reported

(3) Discrepancies between the availability of data and the research described

(4) Inappropriate citations

(5) Incoherent, meaningless and/or irrelevant content included in the article

(6) Manipulated or compromised peer review

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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[1] G. Jian, W. Lin, N. Wang, J. Wu, and X. Wu, "Urine Albumin/Creatinine Ratio and Microvascular Disease in Elderly Hypertensive Patients without Comorbidities," *BioMed Research International*, vol. 2021, Article ID 5560135, 8 pages, 2021.

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Research Article

Urine Albumin/Creatinine Ratio and Microvascular Disease in Elderly Hypertensive Patients without Comorbidities

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Objectives. A high urine albumin/creatinine ratio (UACR) is associated with microvascular disease in hypertensive patients. However, hypertensive patients frequently have other comorbidities. Thus, it is difficult to distinguish the role of UACR from that of comorbidities in microvascular disease. The aim of this study was to evaluate the association between UACR and microvascular disease in elderly hypertension patients without comorbidities. *Methods*. A cross-sectional cohort study of 2252 essential hypertension patients aged 65-94 years without comorbidities between January 1, 2016, and December 31, 2017, was conducted. Microvascular disease was evaluated by hypertension retinopathy (HR). Multivariable adjusted odds of HR by UACR quartiles were determined using logistic regression. *Results*. The HR prevalence was 22.1% ($n = 472$) among the cohort study and was significantly different among UACR quartiles (19.7%, 20.3%, 22.0%, and 26.4% in quartiles 1, 2, 3, and 4, respectively, $P = 0.036$). After adjustment for covariates, higher UACR (odds ratio (OR) = 1.42, 95% confidence interval (CI) 1.05-1.92, quartile 4 versus 1) were significantly associated with HR. Among male patients, higher UACR (OR = 1.65, 95% CI 1.07-2.55, quartile 4 versus 1) were significantly associated with HR after adjustment for covariates. Among female patients, however, 64% and 40% increased odds of HR were noted in the highest and lowest UACR (quartiles 4 and 1, respectively) compared to UACR quartile 2. *Conclusions*. Microvascular disease was associated with higher UACR in elderly male essential hypertension patients without comorbidities but was associated with lower and higher UACR in female patients without comorbidities.

1. Introduction

Hypertension is a growing global health problem and a significant risk factor for the development of various cardiovascular diseases, including coronary heart disease, stroke, microvascular disease (MVD), and chronic kidney disease [1–4]. MVD is considered a crucial pathway in the development and progression of cardiometabolic and renal disease and is associated with increased cardiovascular mortality [5]. In the general population, age, sex, hypertension, dyslipidemia, hyperglycemia, obesity, albuminuria, and smoking are significant determinants of MVD [6–10]. It is well known that MVD is the result of hypertension [11, 12]. Patients with hypertension often suffer from other comorbidities, such as diabetes, dyslipidemia, hyperglycemia, obesity, and proteinuria, and harmful habits such as smoking and drinking. Thus, it is difficult to distinguish the role of these risk factors from that of comorbidities in MVD.

A meta-analysis study reported that albuminuria was associated with cerebral small vessel disease, indicating shared MVD in the kidney and the brain [10]. Another study from the United Kingdom also reported that albuminuria is associated with a narrower and wider arteriolar caliber in patients aged 45-84 years without baseline clinical cardiovascular disease [13]. However, patients with diabetes or smoking were not excluded in these studies. Therefore, it is difficult to distinguish the role of albuminuria from that of comorbidities in MVD. In the present study, to reduce the effect of comorbidities and harmful habits on MVD, we included those without comorbidities and free of current smoking and drinking. Besides, an elevated urine albumin/-creatinine ratio (UACR) below the proteinuria level, i.e., microalbuminuria, has long been recognized as a marker of kidney disease and increased cardiovascular risk, and MVD is a consequence of hypertension and elderly age was associated with MVD [11, 12, 14]. To reduce the effect of hypertension and elderly age on MVD, we only included elderly age patients with hypertension. Thus, we aimed to evaluate the association between UACR and MVD in elderly Chinese hypertensive patients without comorbidities.

2. Materials and Methods

2.1. Study Population. The study was a cross-sectional cohort study of 2252 men and women aged 65-94 years (mean age 71.8 years), without clinical comorbidities, recruited from the Gumei community (Minhang District, Shanghai, China) between January 1, 2016, and December 31, 2017. This study was designed to investigate the prevalence of MVD and its predictors. Elderly essential hypertension patients with symptoms or a history of medical or treatment for comorbidities were excluded. Patients with current smoking or drinking were also excluded. Patients with eGFR less than 60 mL/min/1.73 m^2 may possibly develop vascular dysfunctions and complications [15, 16]. Thus, we also excluded those with eGFR < 60 mL/min/1.73 m^2. No patients were involved in setting the research question or outcome measures or were involved in the design or implementation of the study. This study was conducted according to the principles expressed in the Declaration of Helsinki. The Ethics Committees of the Gumei Community Health Center approved the protocol of this cross-sectional study and waived the need for written informed consent because the data were analyzed anonymously.

2.2. Urine Albumin/Creatinine Ratio. The patients provided basic health information and a spot urine specimen generally immediately after arriving in the morning at the Gumei Community Health Center. Urine albumin and creatinine were measured at the Clinical Chemistry Laboratory at the Affiliated Sixth People's Hospital, Shanghai Jiao Tong University. A spot UACR in milligrams/grams was then calculated for all patients. Patients with reasons for a false-positive UACR test were excluded. Albuminuria was then defined as a UACR ≥ 30 mg/g for men and women. This definition includes both microalbuminuria (UACR ≥ 30-299 mg/g) and macroalbuminuria (UACR ≥ 300 mg/g) [13].

2.3. Retinal Photography. The retinal microvasculature reflects cumulative small vessel damage from hypertension and other vascular processes [12]. Thus, in the present study, MVD was evaluated by retinal photography. Retinal photography was performed using a standardized protocol [17, 18]. A 45-degree 6.3-megapixel nonmydriatic camera was used to photograph the optic discs and macula of both eyes of each subject. These photographs were sent to the Affiliated Sixth People's Hospital, Shanghai Jiao Tong University, for evaluation of retinal pathology. Trained graders were blinded to participant characteristics. The HR classification is based on Mitchell–Wong classification systems [19].

2.4. Covariates. All patients completed self-administered questionnaires and were interviewed and checked by trained researchers. In the morning of the participant's first arrival at the examination, fasting blood and urine samples were collected. Baseline characteristics were recorded, including age, sex, body mass index (BMI), systolic blood pressure (BP), diastolic BP, neutrophil to lymphocyte (N/L) ratio, fasting blood glucose, cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), and estimated glomerular filtration rate (eGFR). Systolic BP and diastolic BP were measured three times, and the average was used as the final value after patients had been seated and resting quietly for more than five minutes with feet on the ground and back supported (OMRON Corporation, Kyoto, Japan) [20]. Hypertension was defined as a systolic BP ≥ 140 mmHg or a diastolic BP ≥ 90 mmHg. Patients currently using antihypertensive medications were also classified as positive for hypertension [21]. BMI was calculated as the weight in kilograms divided by the square of height in meters. Residual renal function was assessed by eGFR using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation [22].

2.5. Statistical Analysis. Missing values for all variables were less than 10% in the present study. The missing data is estimated using the missForest method, which is a nonparametric method that processes different types of variables simultaneously [23]. Means ± standard deviations and percentages were used to summarize the characteristics of the study sample by UACR quartiles. Continuous and categorical variables were compared across quartiles of UACR using analysis of variance (ANOVA) and chi-square tests, respectively. We used the quartile with the lowest HR prevalence as a reference (quartiles with higher HR prevalence versus quartile with the lowest HR prevalence). Three models were created to assess potential confounding. Three different logistic regression models were examined so that changes in the parameter estimate with the addition of demographic and laboratory factors could be examined. Unadjusted associations were first examined, followed by adjustments for age and sex. Next, BMI, systolic BP, diastolic BP, N/L ratio, fasting blood glucose, cholesterol, triglycerides, HDL-c, LDL-c, and eGFR were added to examine whether the association of the UACR quartiles with HR was independent of confounding factors. Models were then repeated in the male and female patients. Statistical analyses were performed using the R package 3.6.0 (https://www.r-project.org/).

3. Results

3.1. Baseline Characteristics. Of the 2252 patients, 112 had eGFR < 60 mL/min/1.73 m^2, leaving 2140 for this analysis. Of 2140 patients with the mean age of 71.8 ± 5.6 years, 48.8% were male. UACR ranged from 0.4 to 1123.7 mg/g in the cohort study. Patients with UACR were classified into quartiles: quartile 1 < 10.5 mg/g, quartile 2 = 10.5-19.5 mg/g, quartile 3 = 19.6-36.5 mg/g, and quartile 4 ≥ 36.6 mg/g. The characteristics of the study patients by UACR quartiles are shown in Table 1.

Patients with the highest UACR (quartile 4) had higher systolic BP, diastolic BP, fasting blood glucose, triglycerides, and HDL-c but lower eGFR compared to patients in the lower UACR quartiles 1-3. Table 2 shows the characteristics of male and female patients by UACR quartiles.

Similar differences of characteristics among UACR quartiles were observed in male and female patients. The characteristics of the study patients by sex are shown in Table 3.

3.2. The HR Prevalence. Figure 1 shows the HR prevalence by UACR quartiles among the patients.

The HR prevalence was 22.1% ($n = 472$) in the cohort population. The HR prevalence was highest in quartile 4 (26.4%) and lowest in quartile 1 (19.7%). Among male patients, the HR prevalence also was highest in quartile 4 (27.5%) and lowest in quartile 1 (17.4%). However, among female patients, the HR prevalence was highest in quartile 4 (25.4%) but lowest in quartile 2 (17.4%).

3.3. The Association between UACR and HR. Table 4 shows the results of the logistic regression analyses for UACR quartiles.

Among the cohort study, higher UACR (quartile 4) was associated with 46% increased odds of HR compared to UACR quartile 1 in the unadjusted model (model 1). Further adjustment for demographic and laboratory factors mildly reduced the parameter estimate. In the fully adjusted model (model 3), higher UACR (quartile 4) was associated with 42% increased odds of HR compared to UACR quartile 1 (95%confidence interval (CI) 1.05-1.92).

3.4. The Association between UACR and HR Stratified by Sex. Albuminuria prevalence (UACR ≥ 30.0 mg/g) was not significantly different between men (30.6%) and women (31.8%), and the presence of albuminuria was not significantly associated with sex (male versus female, OR = 1.06, 95% CI 0.88-1.27). Interaction terms showed no significant modification by sex on the association between UACR and HR. However, due to the established clinical importance that sex holds for the risk of HR, we further explored the association between UACR quartiles and the presence of HR in analyses in male and female patients (Table 5).

Among male patients, similar trends were observed compared to associations noted in the cohort study with the highest UACR quartile 4 associated with an increased odd of HR compared to the lowest UACR quartile 1. Among male patients, higher UACR (quartile 4) was associated with 65% increased odds of HR compared to UACR quartile 1 (95% CI 1.07-2.55) in the fully adjusted model (model 3). However, among female patients, when using quartile 1 as a reference, we did not find the association between UACR and HR (data not shown). Nonetheless, among female participants, the HR prevalence was lowest in quartile 2 (17.4%). When using quartile 2 as a reference, higher UACR (quartile 4) was associated with 61% increased odds of HR in the unadjusted model (model 1). In the fully adjusted model (model 3), higher UACR (quartile 4) remained to be associated with 61% increased odds of HR compared to UACR quartile 2 (95% CI 1.06-2.45). Besides, 40% increased odds of HR were noted in the lowest UACR (quartile 1) compared to UACR quartile 2.

4. Discussion

In this study, we found that higher UACR was independently associated with an increased prevalence of HR in elderly male hypertensive patients without comorbidities. Besides, we noted a U-shaped distribution of HR prevalence across the range of UACR with the higher prevalence of HR consistently seen among female patients with higher or lower UACR. In part, this may be explained because sex differences in demographics might explain the observed differences in the prevalence of HR between men and women.

HR is thought to be microvascular damage caused by aging, hypertension, and other processes, reflecting endometrial thickening and medial hyperplasia, transparency, and sclerosis [24]. Because similar pathological features are also seen in the coronary and renal arterioles in patients with hypertension, changes in the retinal arterioles may provide useful information about the state of systemic microcirculation in health and disease [25]. In the present study, therefore, we used HR to evaluate MVD. The independent association between UACR and HR likely reflected microvascular processes in elderly hypertensive patients without comorbidities. For the first time, to minimize the effect of comorbidities and harmful habits on MVD, we excluded those with comorbidities and harmful habits. Thus, the independent associations between UACR and MVD may be more reliable and convincing than those reported by previous studies [10, 13]. A study from the United Kingdom examined the association between retinal arteriolar and venular caliber and the presence of albuminuria (micro- or macroalbuminuria) among participants aged 45-84 years without baseline clinical cardiovascular disease [13]. The authors reported that albuminuria is associated with a narrower and wider arteriolar caliber. Nonetheless, they did not exclude those with hypertension, diabetes, or harmful habits, which suggested that associations between the arteriolar caliber and the presence of incident albuminuria may be mediated by hypertension, diabetes, and harmful habits. Another study examined the association between retinal vascular diameter and chronic kidney disease in a population-based cohort of 3280 community-dwelling adults aged 40-80 years living in Singapore. The authors reported that MVD was also found to be positively associated with both eGFR and micro/macroalbuminuria [26]. Similarly, patients with diabetes, drinking, or smoking were not excluded, which may lead to under- or overestimation of the association between MVD and micro/macroalbuminuria.

To date, the association between sex and albuminuria is inconsistent in the previous studies [27, 28]. Men and Blacks have a higher UACR than do women and Whites and may thereby have an increased risk of microvascular and macrovascular disease [27]. However, another study

Table 1: Characteristics and Mitchell–Wong classification in the cohort study by quartiles of UACR.

	Quartile 1 ($n = 534$)	Quartile 2 ($n = 538$)	Quartile 3 ($n = 533$)	Quartile 4 ($n = 535$)
Age (years)	71.8 ± 5.5	71.3 ± 5.5	72.1 ± 5.7	71.9 ± 5.8
Male (%)	264 (49.4)	262 (48.7)	263 (49.3)	255 (47.7)
BMI (kg/m^2)	21.9 ± 3.2	21.9 ± 3.1	21.9 ± 3.1	22.3 ± 3.5
Systolic BP (mmHg)	136.7 ± 17.4	139.0 ± 17.5	142.1 ± 17.6*	145.8 ± 15.8*
Diastolic BP (mmHg)	79.3 ± 10.6	79.2 ± 10.4	81.0 ± 11.0*	81.5 ± 11.9*
N/L ratio	1.77 ± 0.89	1.77 ± 0.73	1.84 ± 1.05*	1.79 ± 0.92
Fasting blood glucose (mg/dL)	98.4 ± 17.0	104.6 ± 16.1*	106.7 ± 19.5*	110.0 ± 24.0*
Cholesterol (mg/dL)	202.5 ± 37.1	206.3 ± 38.5	207.3 ± 41.8	208.8 ± 42.7*
Triglycerides (mg/dL)	132.6 ± 98.9	138.9 ± 77.6	147.5 ± 85.4*	147.6 ± 87.6*
HDL-c (mg/dL)	61.0 ± 13.1	64.6 ± 14.7*	63.6 ± 13.5*	64.8 ± 14.3*
LDL-c (mg/dL)	113.8 ± 30.1	112.6 ± 29.9	113.5 ± 31.2	113.0 ± 32.0
eGFR (mL/min/1.73 m^2)	90.8 ± 20.7	87.7 ± 18.8	80.0 ± 19.0*	78.5 ± 18.3*
Mitchell–Wong classification				
None (%)	429 (80.3)	429 (79.7)	416 (78.0)	394 (73.6)
Mild (%)	98 (18.4)	90 (16.7)	104 (19.5)	118 (22.1)
Moderate (%)	7 (1.3)	16 (3.0)	13 (2.4)	19 (3.6)
Malignant (%)	0 (0.0)	3 (0.6)	0 (0.0)	4 (0.7)

*$P < 0.05$ compared to quartile 1. UACR: albumin/creatinine ratios; BMI: body mass index; BP: blood pressure; N/L: neutrophil to lymphocyte ratio; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; eGFR: estimated glomerular filtration rate.

Table 2: Characteristics and Mitchell–Wong classification in elderly male and female patients by quartiles of UACR.

	Male				Female			
	Quartile 1 ($n = 264$)	Quartile 2 ($n = 262$)	Quartile 3 ($n = 263$)	Quartile 4 ($n = 255$)	Quartile 1 ($n = 270$)	Quartile 2 ($n = 276$)	Quartile 3 ($n = 270$)	Quartile 4 ($n = 280$)
Age (years)	72.2 ± 5.7	71.2 ± 5.2	72.5 ± 5.9	72.5 ± 5.8	71.5 ± 5.4	71.4 ± 5.7	71.7 ± 5.6	71.3 ± 5.7
BMI (kg/m^2)	21.8 ± 3.2	21.9 ± 2.9	22.0 ± 3.1	22.4 ± 3.3	22.0 ± 3.2	22.0 ± 3.2	21.9 ± 3.1	22.3 ± 3.7
Systolic BP (mmHg)	135.2 ± 16.6	139.5 ± 17.4	142.8 ± 18.0*	145.1 ± 19.0*	138.1 ± 18.1	138.4 ± 17.5	141.5 ± 17.2	146.4 ± 18.7¶
Diastolic BP (mmHg)	78.1 ± 10.2	79.3 ± 10.8	81.0 ± 10.9	81.1 ± 12.5*	80.4 ± 10.8	79.1 ± 10.0	81.1 ± 11.1	82.0 ± 11.3¶
N/L ratio	1.72 ± 0.71	1.77 ± 0.73	1.84 ± 1.05	1.84 ± 1.16	1.82 ± 1.04	1.74 ± 0.69	1.89 ± 1.31	1.74 ± 0.63
Fasting blood glucose (mg/dL)	98.1 ± 16.6	104.8 ± 16.3*	106.0 ± 17.3*	110.6 ± 25.1*	98.7 ± 17.4¶	104.4 ± 16.0	107.4 ± 21.4	109.5 ± 22.9¶
Cholesterol (mg/dL)	201.8 ± 39.3	206.7 ± 37.3	209.0 ± 41.5*	207.8 ± 42.5	203.2 ± 34.9	205.9 ± 39.8	205.6 ± 42.0	210.0 ± 43.0
Triglycerides (mg/dL)	135.5 ± 112.9	140.4 ± 84.6	149.8 ± 90.6	148.9 ± 96.0	129.8 ± 83.0	137.4 ± 70.5	145.3 ± 80.1	146.4 ± 79.3
HDL-c (mg/dL)	60.4 ± 14.2	64.5 ± 14.5*	64.2 ± 12.6*	64.4 ± 14.0*	61.7 ± 13.1¶	64.6 ± 14.9	63.0 ± 14.3	65.1 ± 14.6
LDL-c (mg/dL)	113.5 ± 32.7	120.7 ± 35.4	114.0 ± 31.4	111.9 ± 32.7	114.1 ± 27.3	111.7 ± 30.7	113.1 ± 31.1	113.9 ± 31.4
eGFR (mL/min/1.73 m^2)	89.9 ± 19.2	86.7 ± 35.4	83.7 ± 17.4*	79.5 ± 16.7*	87.9 ± 18.6	89.0 ± 19.3	82.9 ± 18.7¶	78.4 ± 17.9¶
Mitchell–Wong classification								
None (%)	218 (82.6)	201 (76.7)	204 (77.6)	185 (72.5)	211 (78.1)	228 (82.6)	212 (78.5)	209 (74.6)
Mild (%)	44 (16.7)	47 (17.9)	52 (19.8)	56 (22.0)	54 (20.0)	43 (15.6)	52 (19.3)	62 (22.1)
Moderate (%)	2 (0.8)	12 (4.6)	7 (2.7)	11 (4.3)	5 (1.9)	4 (1.4)	6 (2.2)	8 (1.9)
Malignant (%)	0 (0.0)	2 (0.8)	0 (0.0)	3 (1.2)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.4)

*$P < 0.05$ compared to quartile 1; ¶$P < 0.05$ compared to quartile 2. UACR: albumin/creatinine ratios; BMI: body mass index; BP: blood pressure; N/L: neutrophil to lymphocyte ratio; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; eGFR: estimated glomerular filtration rate.

Table 3: Characteristics and Mitchell–Wong classification stratified by sex.

	Male (n = 1044)	Female (n = 1096)	P value
Age (years)	71.8 ± 5.5	71.3 ± 5.5	0.139
BMI (kg/m^2)	21.9 ± 3.2	21.9 ± 3.1	0.915
Systolic BP (mmHg)	136.7 ± 17.4	139.0 ± 17.5	0.031
Diastolic BP (mmHg)	79.3 ± 10.6	79.2 ± 10.4	0.884
N/L ratio	1.77 ± 0.89	1.77 ± 0.73	0.992
Fasting blood glucose (mg/dL)	98.4 ± 17.0	104.6 ± 16.1	<0.001
Cholesterol (mg/dL)	202.5 ± 37.1	206.3 ± 38.5	0.105
Triglycerides (mg/dL)	132.6 ± 98.9	138.9 ± 77.6	0.252
HDL-c (mg/dL)	61.0 ± 13.7	64.6 ± 14.7*	<0.001
LDL-c (mg/dL)	113.8 ± 30.1	112.6 ± 29.9	0.937
eGFR (mL/min/1.73 m^2)	89.8 ± 30.1	86.8 ± 29.9	0.027
UACR (mg/g)	5.70 ± 2.95	14.64 ± 2.60	<0.001
Albuminuria (%)	319 (30.6)	348 (31.8)	0.575
Mitchell–Wong classification			
None (%)	808 (77.4)	860 (78.5)	0.556
Mild (%)	199 (19.1)	211 (19.3)	0.913
Moderate (%)	32 (3.1)	23 (2.1)	0.173
Malignant (%)	5 (0.5)	2 (0.2)	0.363

UACR: albumin/creatinine ratios; BMI: body mass index; BP: blood pressure; N/L: neutrophil to lymphocyte ratio; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; eGFR: estimated glomerular filtration rate. Female patients had higher systolic BP, fasting blood glucose, HDL-c, and UACR but lower eGFR compared to male patients.

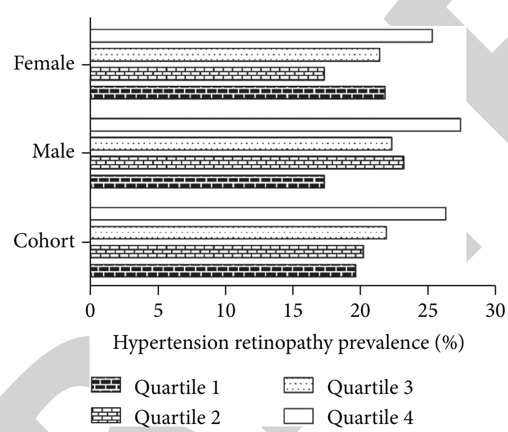

Figure 1: Prevalence of hypertension retinopathy by UACR quartiles and by the presence of sex. UACR: urine albumin/creatinine ratio.

showed that in the multivariate-adjusted model, female sex (OR = 1.62; 95% CI 1.29-2.05) was independently associated with microalbuminuria [28]. In the present study, albuminuria prevalence was not significantly different between men and women and the presence of albuminuria was not significantly associated with sex. These findings in our study may be more reliable due to excluding those with comorbidities or harmful habits, which may reduce the effect of comorbidities and harmful habits on the association between albuminuria and sex.

The prevalence, progression, and pathophysiology of both MVD and macrovascular disease are different in the two sexes [29–32]. Nonetheless, there are few studies focusing on sex-dependent differences in the association between UACR and MVD. In the present study, we found that there were sex-dependent differences in the association between UACR and MVD. Among male patients, the highest UACR (quartile 4) had a 1.65-fold risk of MVD compared to the lowest UACR (quartile 1) after adjustment for covariates. Among female patients, however, the highest and lowest UACR (quartiles 4 and 1) had 1.64- and 1.40-fold risk of MVD compared to UACR quartile 2. Therefore, among men patients, higher UACR was independently associated with an increased prevalence of MVD, but a U-shaped distribution of MVD prevalence across the range of UACR with the higher prevalence of MVD consistently was seen among female patients with higher or lower UACR.

The strength of our study was to reduce the effect of comorbidities and harmful habits on MVD, and we excluded those elderly hypertensive patients with comorbidities or harmful habits. Thus, these findings may be more reliable and convincing in our study. There are some limitations of this work to be noted. First, we did not exclude those with macroalbuminuria, which may lead to selective bias. Because the causes of macroalbuminuria may be attributed to other diseases rather than hypertension, the selective bias may under- or overestimate the prevalence of MVD. Secondary, we have not documented antihypertensive drugs, such as renin-angiotensin, which play a crucial role in the treatment of albuminuria. Finally, because this is a cross-sectional

Table 4: Adjusted odds ratio for hypertension retinopathy by quartiles of UACR.

	Model 1 OR (95%)	P	Model 2 OR (95%)	P	Model 3 OR (95%)	P
Cohort ($n = 2140$)						
Quartile 1	1.0 (reference)		1.0 (reference)		1.0 (reference)	
Quartile 2	1.04 (0.78-1.40)	0.807	1.04 (0.77-1.40)	0.807	1.06 (0.78-1.44)	0.700
Quartile 3	1.15 (0.86-1.55)	0.357	1.15 (0.86-1.55)	0.357	1.20 (0.89-1.63)	0.309
Quartile 4	1.46 (1.10-1.95)	0.010	1.46 (1.10-1.95)	0.010	1.42 (1.05-1.92)	0.025
P for trends	<0.001		<0.001		<0.001	

Model 1: unadjusted. Model 2: adjusted for age and sex. Model 3: model 2 adjusted for BMI, systolic BP, diastolic BP, N/L ratio, fasting blood glucose, cholesterol, triglycerides, HDL-c, LDL-c, and eGFR. UACR: albumin/creatinine ratios; BMI: body mass index; BP: blood pressure; N/L: neutrophil to lymphocyte ratio; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; eGFR: estimated glomerular filtration rate; OR: odds ratio; CI: confidence index.

Table 5: Adjusted odds ratio for hypertension retinopathy by quartiles of UACR and by sex.

	Model 1 OR (95%)	P	Model 2 OR (95%)	P	Model 3 OR (95%)	P
Male ($n = 1044$)						
Quartile 1	1.0 (reference)		1.0 (reference)		1.0 (reference)	
Quartile 2	1.43 (0.94-2.21)	0.096	1.43 (0.94-2.21)	0.096	1.39 (0.90-2.15)	0.136
Quartile 3	1.37 (0.89-2.11)	0.121	1.37 (0.89-2.11)	0.121	1.27 (0.82-1.98)	0.290
Quartile 4	1.79 (1.18-2.73)	0.006	1.79 (1.18-2.73)	0.006	1.65 (1.07-2.55)	0.024
P for trends	<0.001		<0.001		<0.001	
Female ($n = 1096$)						
Quartile 1	1.33 (0.87-2.03)	0.190	1.33 (0.87-2.03)	0.190	1.40 (0.91-2.16)	0.127
Quartile 2	1.0 (reference)		1.0 (reference)		1.0 (reference)	
Quartile 3	1.30 (0.85-1.99)	0.228	1.30 (0.85-1.99)	0.228	1.34 (0.87-2.07)	0.1.77
Quartile 4	1.61 (1.07-2.44)	0.023	1.61 (1.07-2.44)	0.023	1.61 (1.06-2.45)	0.025
P for trends	<0.001		<0.001		<0.001	

Model 1: unadjusted. Model 2: adjusted for age and sex. Model 3: model 2 adjusted for BMI, systolic BP, diastolic BP, N/L ratio, fasting blood glucose, cholesterol, triglycerides, HDL-c, LDL-c, and eGFR. UACR: albumin/creatinine ratios; BMI: body mass index; BP: blood pressure; N/L: neutrophil to lymphocyte ratio; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; eGFR: estimated glomerular filtration rate; OR: odds ratio; CI: confidence index.

cohort, we cannot exclude the possibility of residual or unmeasured confounding. A further prospective longitudinal study should be conducted to evaluate whether the UACR management may improve the MVD process in elderly hypertensive patients.

In summary, we found that there were sex-dependent differences in the association between UACR and MVD in those elderly hypertensive patients without comorbidities. Among men patients, higher UACR was independently associated with an increased prevalence of MVD, but a U-shaped distribution of MVD prevalence across the range of UACR with the higher prevalence of MVD consistently was seen among female patients with higher or lower UACR. Thus, different UACR management should be conducted for elderly men and women hypertensive patients.

Data Availability

Readers can access the data underlying the findings of the study by contacting the corresponding author.

Conflicts of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contributions

Guihua Jian and Wenjun Lin contributed equally to this work.

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