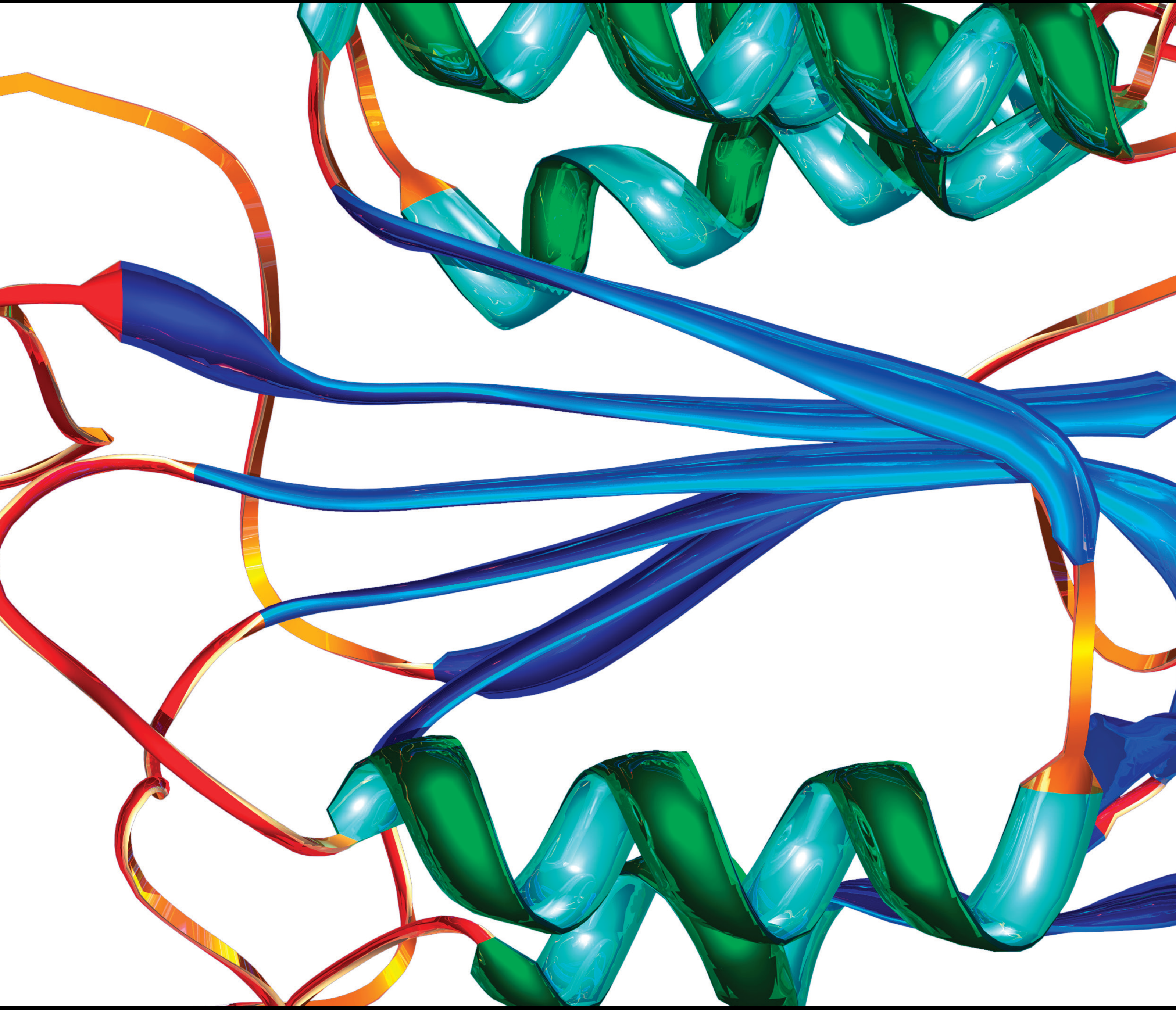
Disease Markers

Optimized Deep Learning Models for Diagnostic Markers

Lead Guest Editor: Vijay Kumar
Guest Editors: Kehui Sun and Kumar Dinesh Kant



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Retraction

Retracted: Senkyunolide H Affects Cerebral Ischemic Injury through Regulation on Autophagy of Neuronal Cells Via P13K/AKT/mTOR Signaling Pathway

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(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) Peer-review manipulation

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.

References

[1] B. Zhao, K. Tang, Y. Zhao, and W. Zhao, "Senkyunolide H Affects Cerebral Ischemic Injury through Regulation on Autophagy of Neuronal Cells Via P13K/AKT/mTOR Signaling Pathway," *Disease Markers*, vol. 2022, Article ID 9211621, 8 pages, 2022.

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Retraction

Retracted: BERT-Based Clinical Name Entity Reorganization Model for Health Diagnosis

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References

[1] Y. D. Borole, A. V. Agrawal, M. Tesfayohanis, D. Thakkar, M. R. Abonazel, and F. A. Awwad, "BERT-Based Clinical Name Entity Reorganization Model for Health Diagnosis," *Disease Markers*, vol. 2022, Article ID 2297063, 12 pages, 2022.

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Retraction

Retracted: The Perspectives of Surrogates and Healthcare Providers Regarding SDM (Shared Decision-Making)

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References

[1] Q. Lu, J. Ji, X. Lu, Q. Yin, and Y. Yang, "The Perspectives of Surrogates and Healthcare Providers Regarding SDM (Shared Decision-Making)," *Disease Markers*, vol. 2023, Article ID 6251492, 10 pages, 2023.

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Retraction

Retracted: A Mixed Methods Investigation of the Prevalence and Influencing Factors of Compassion Fatigue among Midwives in Different Areas of China

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In addition, our investigation has also shown that one or more of the following human-subject reporting requirements has not been met in this article: ethical approval by an Institutional Review Board (IRB) committee or equivalent, patient/participant consent to participate, and/or agreement to publish patient/participant details (where relevant).

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References

[1] X. Liang, P. Yuan, X. Su et al., "A Mixed Methods Investigation of the Prevalence and Influencing Factors of Compassion Fatigue among Midwives in Different Areas of China," *Disease Markers*, vol. 2022, Article ID 1815417, 11 pages, 2022.

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Research Article

The Perspectives of Surrogates and Healthcare Providers Regarding SDM (Shared Decision-Making)

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The purpose of this paper is to explore the attitudes of surrogacy and medical service providers toward SDM and to identify the barriers and promoters of SDM in this population. To this end, we conducted a qualitative study of surrogacy and medical service providers in the First Affiliated Hospital of Soochow University using semistructured interviews. Thirty participants (11 agents, 12 ICU physicians, and 7 ICU nurses) were interviewed. The three stakeholders showed different attitudes toward SDM. They reported barriers to SDM, including insufficient cognition of decision-makers, high expectations, negative psychological experiences, previous decision-making experiences, excessive workload, heavy financial burden, and lack of decision AIDS. They reported facilitators of SDM, including trust, effective communication, decision support, value clarification, outcome commitment, and continuous service. This study explored the different attitudes of the three stakeholders and identified various barriers and facilitators of SDM. It highlights the need to develop localised decision AIDS and to involve agents and nurses more in the decision-making process. Therefore, this paper identifies barriers and facilitators of SDM in this population. In addition, the study identified various barriers and facilitators to SDM and highlighted the need to develop localised decision AIDS and involve agents and nurses more in the decision-making process. Finally, the barriers and facilitators of SDM are established. The paper also shows that the development of localized decision AIDS and greater involvement of agents and nurses in the decision-making process are integral to good treatment outcomes.

1. Introduction

Because of the development of society and medicine, people's awareness of health protection and participation in the process of disease diagnosis and treatment are constantly improving. At the same time, it also promotes the concept of shared decision (SDM). After more than 40 years of research and clinical practice, shared decision-making has become quite mature in developed countries such as Europe and the United States. In 2016, the ethics committees of the American College of Critical Care Medicine (ACCM) and the American Thoracic Society (ATS) recommended the use of SDM to define overall care goals in the ICU. However, at present, family decision-making participation, patient values, and treatment intention are paid less attention in ICUs in China. All these indications indicate that the feasibility and effectiveness of SDM in ICU are the current problems that need to be solved.

2. Background

Stakeholder management is a common expression in business today, but the concept and its practical implications for how stakeholder relationships should be managed and how they should be managed remain at the center of lively discussions across multiple disciplines, notably business ethics, management theory, corporate law, and organizational theory. Freeman defines stakeholders as follows: "In a narrow sense, stakeholders are all identifiable groups or individuals on which an organization depends for survival, sometimes referred to as key stakeholders: shareholders, employees, customers, suppliers, and key government agencies. At a broader level, however, a stakeholder is any identifiable group or individual who can influence or be influenced by an organization's performance in terms of products, policies, and work processes. In this sense, public interest groups, protest groups, local communities, government agencies, trade associations, competitors, trade unions and the media are all organisational stakeholders." Colle De S., [1].

The implementation of shared decision-making (SDM) in the intensive care unit (ICU) embodies the ethical principles of autonomy, nonharm, benefit, and justice [2] orative process that allows patients or their surrogate decision-makers (surrogates) and healthcare providers to make decisions together on the basis of the best scientific evidence available and patients' values, goals, and preferences [3].

In 2016, the American College of Critical Care Medicine (ACCM) and the American Thoracic Society (ATS) ethics committee recommended the use of SDM to define overall care goals which include limiting or withdrawing from life-prolonging interventions and making preference-sensitive treatment decisions [3]). The default SDM approach includes three key stages: information exchange, deliberation, and treatment decision. A well-functioning ICU team comprising ICU physicians, ICU nurses, and other members is critical to the SDM process [4]. It greatly influences improvement of patient outcomes, increase of medical satisfaction, and reduction of medical costs and moral distress of surrogates [5–7].

However, patients' wishes and preferences are not respected, and the prognosis and treatment risks are not discussed in detail; the SDM approach is seldom adapted in the ICU. Scheunemann et al. found that physicians considered patients' values and preferences while making treatment recommendations in only 20 out of 244 conferences (8.2%) [5]. Kruser et al. found that ICU physicians invite family members to participate in SDM only when available medical treatments fail to achieve physiologic goals [8]. These peculiarities of the ICU workplace culture and practice style bring profound challenges to the implementation of SDM. Patients' families and friends assume the role of surrogates while being unsure of the preferences and wishes of coma patients. Therefore, in circumstances wherein the patient cannot be directly involved in treatment decision-making, consulting surrogates for SDM presents with distinct psychological, ethical, and communication challenges. Therefore, a better understanding of barriers and facilitators associated with the implementation of SDM is needed.

Although several factors affecting ICU SDM have been identified by researchers, such as patient/family willingness to participate in the decision-making process, staff expertise, and lack of time, in terms of previous studies, few researchers have explored barriers and facilitators from different SDM stakeholder groups in current ICU care [9, 10]. In addition, due to the participation of family decision-making in ICUs in China, patients' values and treatment intention are less important. To clarify the feasibility and effectiveness of ICU SDM is a problem that needs to be solved at present. Therefore, this study is aimed at exploring the perceptions of SDM among surrogates and healthcare providers (physicians and nurses) and at identifying barriers and facilitators of SDM in these individuals.

3. Methods

3.1. Study Design and Setting. We conducted a qualitative study using semistructured interviews of surrogates and healthcare providers from July 2020 to December 2020 at Suzhou University attached first hospital, which is a large tertiary center and teaching hospital. We chose a qualitative approach rather than a survey. This is to get a deeper understanding and to get the personal views of the participants. Since the need for SDM may be greater between surrogators and healthcare providers in patients with hospital stays longer than 3 days, surrogators were interviewed 3 days after admission [11]. SDM among the three stakeholder groups (physicians, nurses, and surrogators) in the ICU usually occurs (1) during daily multidisciplinary meetings attended primarily by the ICU physician and surrogators, (2) during regular family meetings where the presence of the ICU nurse is preferred but not required, and (3) if it is done in a relatively informal setting. The interview location will be at the bedside [12].

The local institutional review board approved this study. All participants provided written consent.

3.2. Participants. In order to obtain more objective and unbiased findings, three groups of participants recruited from a comprehensive ICU were interviewed: doctors, nurses (healthcare providers), and surrogates. Agents older than or 18 years old (authorized for the study), who were also the primary caregivers of inpatients, were selected to participate in face-to-face interviews. All substitutes reported discussing treatment goals, treatment-related risks, and possible outcomes for hospitalized patients with their healthcare provider prior to the interview. Healthcare providers include cases assigned to ICU inpatients.

3.3. Sampling. Thirty eligible participants (11 surrogates, 12 ICU physicians, and 7 ICU nurses) were interviewed. Although the sampling was based on convenience, we included as many demographic and professional characteristics as possible to ensure the authenticity of the study results. The study included surrogate mothers of different ages, genders, and relationships with patients. Again, we include healthcare providers of different ages, genders, job titles, and work experience.

3.4. Data Collection. The whole interview process of all interviewees is conducted in a private room by themselves, and the interview lasts 30-45 minutes. The interviews explored three themes related to the SDM domain framework (status quo, attitudes, barriers, and facilitators) [13]. According to the feedback from two pilot tests, we adjusted the interview outline to reduce medical jargon. All interviews were conducted by the same researcher (LQ). The researcher was trained in conducting interviews and performing interview analysis. The researcher had not conducted qualitative work on this topic before with the same interviewees. This is because we wanted to preserve the fact that at the beginning of the interview, the researchers introduced respondents to the concept of SDM to ensure that they had a clear understanding of the topic before the interview. This also ensures that they will not be forced to incorporate previous concepts. At the end of the interview, respondents were asked to complete a demographic survey. The interview was recorded. Data collection continues until theoretical adequacy is reached.

3.5. Data Analysis. Two researchers (LQ, JJ) used qualitative content analysis to summarize text responses from 11 agents and 19 healthcare providers [14]. Each researcher independently reviewed the notes word for word, highlighting specific words that seemed to capture key concepts of SDM among respondents and jotting down the main impressions and ideas used to develop the code. The researchers then discussed the emerging code, grouped them to reach consensus, and organized the themes to create meaningful clusters. After the first five transcripts were coded to determine the coding scheme, the agreed codes and themes were systematically applied to all transcripts. Themes, their descriptors, and representative citations were presented to the respondents and reviewed with them to solicit their opinions on whether these aspects correctly reflected their views on SDM.

4. Results

In total, 30 participants including 11 surrogates (Table 1) and 19 healthcare providers (12 ICU physicians and 7 ICU nurses; Table 2) were interviewed; there were no drop-outs. Among the participants, 8/11 surrogates and 6/19 healthcare providers were men. The mean age of surrogates and healthcare providers was 44.1 years (SD (standard deviation): 9.9 years) and 34.8 years (SD: 6.0 years), respectively. Notably, 5/11 patients were hospitalized for a medical condition, 4/11 underwent a planned surgery, and 2/11 underwent an emergency surgery. The median work experience of the 12 ICU physicians was 11 years (IQR (interquartile range): 5.0–28.0), whereas the corresponding statistic for the seven ICU nurses was 9 years (IQR: 2.0–22.0).

The data analysis was divided into 16 categories, and three themes were obtained: (1) different attitudes toward SDM, including the supportive attitude of doctors, the inconsistent attitude of nurses, and the contradictory attitude of agents. The specific content can be viewed in Table 3. (2) The obstacles of SDM, that is to say, the decision-makers have insufficient cognition, high expectation, negative psychological experience, existing decision-making experience, excessive workload, heavy economic burden, and lack of decision-making AIDS. The specific content can be viewed in Table 4. (3) The promoting factors of SDM are trust, effective communication, decision support, value clarification, outcome commitment, and continuous service. The specific content can be viewed in Table 5.

4.1. Theme 1: Different Attitudes toward SDM. When asked about decision-making process and SDM, different stakeholder groups showed different attitudes (Table 3). Physicians argue that the notion that the health care system has somehow evolved into a "patient-centered" approach to medicine has caught on. Internists encourage agents to participate in SDM and believe that they can make treatment decisions that are in the best interest of their patients through mutual consultation. They also point to the need to modify the decision-making process to meet the different needs of agents, especially as some agents prefer to leave the final decision to the physician.

In addition, with the increasing call for "patient participation," nurses reported being constantly aware of the need for patients or their surrogates to participate in the decision-making process and witnessing the gradually increasing popularity of the concept of SDM. However, some nurses were skeptical about the necessity and effectiveness of the implementation of SDM and reported being concerned about the increase in the consumption of manpower and material resources associated with the implementation of SDM in clinical practice.

Surrogates believed that SDM would help them stay informed about different treatment plans and make a relatively clear decision; this would in turn reduce their psychological pressure. However, the premise of SDM was that surrogates perceive the need of SDM. A few surrogates expressed hesitation to participate in the decision-making process and feared that their involvement in the decision-making process will only interfere with physicians' work.

4.2. Theme 2: Barriers of SDM. We identified seven barriers of SDM in this theme (inadequate cognition of decision-makers, high expectation, negative psychological experience, previous decision-making experience, excessive workload, financial burden, and lack of decision aids). First, because of lack of parity in disease knowledge between physicians and patients, a part of the surrogates fell into a "physicians know the best" and "families with inadequate knowledge" category. They thought physicians do not want families to interfere in the treatment or be questioned. They felt that doing so may harm physicians' professional identity or may be perceived as a reflection of mistrust or lack of respect toward the physician. At the same time, some surrogates had unreasonably high expectations of the psychological recovery of the patients after the treatment; therefore, they focused only on the results without comprehensively considering other aspects of the treatment and its outcomes. Their judgments were often not purely rational and were driven by strong emotions. Overly optimistic expectations of surrogates promoted excessive use of invasive treatments and delayed palliative care for terminally ill patients.

Surrogates' psychological experiences of shock and worry and previous negative decision-making experiences also hindered the implementation of SDM. These strong emotions impaired their ability to process information, deliberate, and make trade-offs. In the absence of the patient, the choice of treatment should consider what the will and preference of the patient would have been. Some surrogates showed lack of readiness with making a choice within a short period of time, and therefore, they would seek help from physicians and choose the plan recommended by

Table 1: Surrogate characteristics.

Interview order	Relationship with patient	Age	Gender	Highest education level
F1	Child of patient	47	Male	High school or less
F2	Parents of patient	58	Male	High school or less
F3	Brother of patient	30	Male	Associate's or Bachelor's degree
F4	Child of patient	42	Female	High school or less
F5	Grandchild of patient	32	Female	Associate's or Bachelor's degree
F6	Spouse of patient	31	Male	Associate's or Bachelor's degree
F7	Child of patient	41	Male	High school or less
F8	Son-in-law	54	Male	High school or less
F9	Child of patient	59	Male	High school or less
F10	Parents of patient	42	Female	High school or less
F11	Child of patient	49	Male	High school or less

Table 2: Healthcare provider characteristics.

Interview order	ICU physicians and nurses	Age group	Sex
D1	Intensivist	30–35	Female
D2	Intensivist	35–40	Female
D3	Intensivist	35–40	Female
D4	Intensivist	30–35	Female
D5	Intensivist	35–40	Female
D6	Intensivist	30–35	Female
D7	Intensivist	30–35	Female
D8	Intensivist	50–55	Male
D9	Intensivist	30–35	Male
D10	Intensivist	40–45	Male
D11	Intensivist	40–45	Male
D12	Intensivist	30–35	Female
N1	Intensive care nurse	30–35	Male
N2	Intensive care nurse	30–35	Male
N3	Intensive care nurse	30–35	Female
N4	Intensive care nurse	20–25	Female
N5	Intensive care nurse	25–30	Female
N6	Intensive care nurse	30–35	Female
N7	Intensive care nurse	40–45	Female

them. Some surrogates were too dependent on physicians, which was not conducive to the implementation of SDM. Besides, heavy economic burden of the treatment on family members was the most obfuscating and conflicting aspect affecting the decision-making process. Many surrogates found themselves in a dilemma while making a decision because of economic reasons. Particularly with making end-of-life decisions, life support treatment had to be discontinued due to the critical economic condition of the surrogates who could no longer afford the treatment expenses.

Healthcare providers reported that heavy work load did not allow them enough time to assess whether the ongoing treatment was still in line with patients' best interests or wishes. The daily workload of healthcare providers was high, and the time it would take to share decisions with each surrogate would further increase their work burden. Besides, decision aids are also an important factor affecting the implementation of SDM. Decision aids are effective means to promote surrogates' participation in the decision-making process; they help surrogates reach a decision after careful consideration of both their and patients' perspectives. However, ICUs of domestic hospitals lacked the tools that are typically provided by healthcare providers to help surrogates participate in SDM, and the effectiveness of a few decision aids introduced from abroad was unverified.

4.3. Theme 3: Facilitators of SDM. We identified 6 facilitators of SDM within this theme (trust, effective communication, decision support, value clarification, outcome commitment, and continuous service; Table 5). Both surrogates and healthcare providers believed that trusting in each other will make the decision-making process easier, particularly in the emergency situations. In the acute ICU setting, the stakeholders needed to establish agreement promptly for curing patients. Many physicians said that trust was based on the professional skills and control of the patient's condition. Meanwhile, surrogates viewed trust as one of the main factors affecting their participation in SDM as it helped them express their own wishes, cope with the pressure and challenge of making decisions within a short time in complex situations, and improve their enthusiasm for decision-making.

In conversations about patients' condition and treatment goals, which include a lot of medical jargon, it was important to ensure that surrogates understood these professional vocabularies. By exhibiting empathy and control of the pace of conversation in their communication, physicians can improve surrogates' understanding of professional knowledge and achieve emotional resonance with them, thus making communication smoother and enhancing family members' participation in the decision-making process. Conversely, surrogates' active participation in the decision-making process would reduce if they feel that physicians do not pay enough attention to them and do not have enough time to communicate with them.

If surrogates have many friends and relatives, the primary decision-makers may seek their counsel or ask other healthcare workers for advice before reaching a decision. Although family and friends can facilitate the decision-

Table 3: Theme 1: different attitudes toward SDM.

Subtheme	Codes	Quotes
Physicians' supporting attitudes	"Decision-making requires collaboration," "SDM is conducive to alleviating doctor-patient conflicts," and "making decisions with surrogates"	D6: In clinical practice, I understand that it would be better to have more SDM because in the current treatment environment, doctors will take into account the values and various factors of the patient's family, and thus, SDM will be more suitable. If I am only responsible for conveying simple information and let the family members make their own choices, this would just be a communication. However, we also play a guiding role wherein we explain professional knowledge to patients and help them make decisions with their family members. D2: The choice of family members must be respected, but the conflict between doctors and patients is very serious, particularly for patients admitted to the ICU, and the family members have to make critical decisions regarding whether to intubate and whether to continue rescuing patients. We can only give suggestions, and SDM is good. D8: SDM is good, just like communication, which will help a lot. The main problem is that in China, communication is still not standardized.
Nurses' inconsistent attitudes: Supporting and affirming	"SDM is helpful," "nurses are 24 hours at patients' bedside," and "cooperation with doctors and families"	N1: I have heard of SDM. It can help doctors learn more about the patients' wishes. N7: We spend the most time at the patient's bedside and know what the patient is thinking.
Hesitating and doubting	"Lack of time" and "physician may ignore nurses' advice"	N4: At present, we still get informed consent signed by the patient or their surrogate, which prevents many conflicts between doctors and family members associated with any unfavorable outcome. How to implement SDM? Will there be a lot of trouble?" N5: If all clinical decisions need to be shared, it must take a lot of time; we are usually so busy, and there is often not enough time for this approach.
Surrogates' ambivalent attitudes: Willingness to participate in SDM	"Knowing what is coming and feeling included," "more information means better outcomes," and "feeling confident and secure"	F5: The doctor helped us make decisions and explained each treatment plan clearly. We also had a thorough understanding of the next treatment, which made us feel more secure about the treatment outcomes. F6: I think I can participate in the decision-making and make decisions by myself. After all, it is my relative who is admitted to the hospital. Although the doctor is also very important, I can feel relieved if I decide on my own.
No perceived need for SDM	"No attention for the family" and "lacking a feeling of control"	F9: You can decide whether to insert or not (endotracheal intubation) according to your professional expertise. F11: Although you explained everything, we cannot understand exactly what you were saying about surgery. We do not know what decide based on this information. We just have to accept what you are saying, right?

making process, disagreements among family members can delay the process. Many surrogates believed that peer support can better prepare patients for SDM.

In the decision-making process, value clarification was a process of identifying pros and cons, weighing the risks, and sorting the outcome-influencing factors by their importance. The treatment of choice had to align with what the patient would have wanted and preferred. In this process, physicians would actively inquire about and respect patients' wishes. Since most critically ill patients are not able to clearly express their values and preferences, without value clarification, it becomes difficult for doctors and surrogates to reach a consensus on the best treatment strategy and make correct decisions in line with the values and preferences of the patients. In critically ill patients, physicians often fully respect the will of patients and decide a treatment method consistent with patients' preferences after communication with surrogates.

Taken together, healthcare providers and surrogates shared the responsibility of making decisions. Surrogates reported that negotiation with healthcare providers often helped them reach a mutually agreeable decision,

Table 4: Theme 2: barriers of SDM.

Subtheme	Codes	Quotes
Inadequate cognition of decision-makers	"Expecting doctors to make decision," "be an obedient patient," and "doctors are more professional"	F1: There's nothing I can do; it is up to you to save us. We do not understand this stuff. We do not know what you are talking about. We just agree with your treatment. After all, doctors are the most professional. We trust doctors. F6: Because we are unprofessional and doctors are professional, the doctors of course do the right thing. Because we are not professionals, we do not know much about it, but the doctors are doing the right thing. N2: Most family members do not have medical knowledge. When they go to the hospital, they have to follow the doctor's advice; some of them only know a little about it from the Internet, and that's even worse.
High expectation	"Hope to be cured," "not give up," and "do our best to try"	F2: We want the doctor to give us a clear treatment plan and explain in detail how the treatment is going to work. What is it going to take to cure him? F5: My message is very clear—as long as she has a breath, we must hold on. N4: Take the current bed 9 for example. We all know it is hard to cure him, but if the family members do not give up, there is nothing we can do.
Negative psychological experience	"Struggle to make decision," "feel little hope and confused," "fear a loss of control"	F3: I really do not know, I was quite emotional at the time, I did not read it carefully, and I forgot what I said. I'm so nervous, I'm so worried, I cannot remember what we talked about. F10: I forgot a little bit. To tell you the truth, I was also a little emotional at that time. I must have been worried about the children being sent here, and I also forgot the main details I talked about at that time.
Previous decision-making experience	"Have admitted to ICU before," "heard the bad news," and "without confidence to make decision"	F5: My dad was admitted to your ICU once; he had high creatinine, and he was there for a long time. Earlier, he was younger, so he came back, but now he cannot control himself. You tell him to drink less, but he cannot control himself. F7: Yesterday, I was in a bad mood because an old man in our family had an endotracheal tube inserted and died during extubation. I do not know what the problem was. So, this is a place that jangles my nerves. When the doctor called me and asked if he should intubate, I said no.
Excessive workload	"Doctors are too busy," "the medical system does not support SDM," and "too much work limits the conversation about treatment"	F3: Doctors are busy, and SDM takes too much time. F7: It can be difficult to find a doctor sometimes because the system is different. We looked for the doctor and waited a long time for a consultation; the door opened and we were told that the doctor was busy. Then, he told us to wait for a while. Sometimes the doctor came, and sometimes the busy doctor forgot. N5: Every morning from 9:00 to 12:00, a lot of treatment and basic care tasks are ongoing; there is no time to do this. I feel it is not possible to incorporate SDM in ICUs in China.
Financial burden	"Cannot afford the treatment," "have to give up the treatment because of money problems"	D1: For example, financial problems. Some family members feel they can no longer support themselves financially, so they discontinue treatment. D2: For example, a patient who has not urinated needs to undergo hemodialysis, which is associated with high treatment costs. If the family cannot bear the financial pressure, they have to opt for diuretics or other solutions. N3: Some decisions for patients are obviously good, but they come with some financial difficulties. In fact, everyone

Table 4: Continued.

Subtheme	Codes	Quotes
		loves their family, and they all want to get the best treatment for their family members, but some people, after all, are limited by their economic condition, which is one of the biggest factors for treatment discontinuation, and some people may also not have that much time and energy.
Lack of decision aids	"Appropriate tools make decision easier" and "lack the aids to make decision"	D5: Sometimes you talk to family members for a long time, but they still do not know what you are talking about. It's just a waste of time, and there are no appropriate tools in clinical practice. N4: For example, for deep vein catheterization and endotracheal intubation, the family members do not know what kind of tube it is and how thick it is. How can they make decisions? N6: If there are pictures or some simple, easy-to-understand animations of procedures performed in clinical practice, they can be understood by family members at a glance and will facilitate smoother conversations during SDM.

particularly for end-of-life decisions. In addition, because of the shift system in the ICU, healthcare providers change with changing shifts; this may limit healthcare providers' understanding of the needs of patients and their surrogates. Detailed briefing of the new staff about these needs during shift change can help physicians quickly understand the circumstances, and therefore, good medical service continuity between shifts is conducive to the implementation of SDM.

5. Discussion

This qualitative interview study explored the perspectives of the three stakeholders—ICU physicians, ICU nurses, and surrogates—on SDM. Similar to earlier studies, the concept of SDM has started gaining wide recognition, and most healthcare providers strongly acknowledged the significance of SDM [10, 15]. However, a few interviewees still did not clearly understand SDM and confused it with the traditional "informed consent model." In particular, to some extent, nurses lacked clarity regarding their roles and responsibilities in SDM. ICU nurses of domestic hospitals rarely participated in SDM [16]. Similarly, surrogates do not yet understand the concept of SDM or its advantages. Therefore, they struggle with realizing the differences in their decision-making authority according to the gravity of patients' medical conditions; they also struggle with timely decision-making under high-pressure situations. The implementation of SDM needs to be based on the participation of both healthcare providers and surrogates. Some previous studies show that the traditional Chinese culture greatly influences surrogates' decision-making approach; they prefer to play a passive role in decision-making and wish for physicians to decide for them ([17]; Y. D. [18]). Thus, healthcare providers should correct this erroneous approach of surrogates and encourage them to actively contribute to the decision-making process.

In total, the three stakeholders focus on the end-of-life decision as the main decision for which SDM should be implemented. This study found that the surrogates struggled with making end-of-life decisions, which is in agreement with a previous report [5]. In terminal cases, the surrogates felt a sense of loss, anxiety, and denial, thus compromising their mental clarity for making a decision. Some surrogates could not accept the current treatment results of the patients and descended into a mindset of self-reproach; they often had a contradictory and obfuscating outlook toward their own decisions. Although it is widely recognized that SDM involves healthcare providers and surrogates reaching a consensus on a responsible decision, these decisions often involve lesser participation of and inputs from surrogates, particularly in families with inadequate educational levels [19]. Therefore, it is necessary to discuss the barriers and facilitators of the implementation of SDM.

This study identifies several barriers obstructing seamless implementation of SDM in the ICU setting. Based on the interview responses, we identified heavy workload and insufficient communication time of healthcare providers as obstacles affecting the implementation of SDM. In a previous study, insufficient communication time and interruption of intervention were identified as major obstacles faced by ICU healthcare providers for implementing SDM [20]. Lots of research institutions are constantly refining the implementation process of SDM and developing different decision aid tools. In China, using decision aids for patients on long-term mechanical ventilation, researchers helped the surrogates better comprehend medical knowledge and reported that this interaction reduced surrogates' decision-making dilemmas and uncertainty caused by anxiety, depression, and other symptoms (B. B. [21]). Presently, the SDM process is not standardized and localized decision aids are unavailable in China. Hospitals should draw learnings from foreign theoretical frameworks (e.g., Ottawa Decision Support Framework) which develop a robust implementation process for SDM, clearly define the core functions of healthcare providers in SDM, and develop decision aids that would be suitable for the Chinese population and medical system.

Table 5: Theme 3: facilitators of SDM.

Subthemes	Codes	Quotes
Trust	"Trust comes from healthcare providers' professional level," "trust facilitates SDM," and "trust makes communication smoother"	D4: Patients' trust comes from your understanding of their condition and professional level, which is the most important factor for patients to trust you the first time. Only after they trust you can they speak freely with you and effectively make shared decisions with you. N6: The final decision is a matter of trust in doctors. Family members trust doctors, and thus, they can communicate with each other easily, and the treatment will be much smoother. On the other hand, because of access to unverified medical media on the internet that is presented as factually correct information, some medical disputes are exaggerated, which lead to the tension between doctors and patients. F2: I'm sure we trust you, and that's why we are here. We were prepared before we came to the ICU, so we gave it a try.
Effective communication	"Control the pace of conversation" and "put yourself in the patient's shoes"	D1: In short, it is important to reach a state wherein two people can sympathize with each other. Sometimes we are talking about our professional knowledge, but the family members cannot understand it completely. So, the ability to empathize is important. The other thing, which is about keeping a humane approach, is that when talking about an illness, we often try to control the pace in which the information is conveyed based on the family's ability to process and understand the information, and thus, the pace is very important. D12: First, I think I should be professional in my conduct and the judgment of the illness. In addition, I can put myself in the other's shoes. From the point of view of family members, I can understand their psychological condition and communicate better accordingly.
Decision support	"Decision support from others," "suggestions from friends, family and healthcare providers"	F2: I consulted family members before making a decision. It is a big deal. Who would think of drinking like that at a young age? After talking to them, I feel more confident. F4: My family has been discussing it for two or three days. Now we basically know the cause of the disease and the condition. We have made a good decision according to the situation. N5: Even my neighbors sometimes ask my opinion on whether there is a need for hospitalization.
Value clarification	"The doctor gave full consideration to the patient's opinions," "doctors seek the patient's preferred treatment," and "respect the patient's opinion"	D5: Yes, it is also related to his (a family member's) views. If the family member is very active, the doctor will be more active and take active measures because there is no one way to save the patient's life for sure. F9: Doctors also asked our family members for our opinions. They respected our opinion. N4: In fact, sometimes I think I have thought on behalf of the family members, but we are not family members. Although we can try our best to think for them, we may never be able to feel for them as much as a family member would. Everybody's situation is different, and everybody's family dynamics are different, right?
Outcome commitment	"Stopping treatment is a shared choice" and "accept the results together"	F4: We've been debating for days whether to send him home or not. He was awake earlier and spoke with us clearly, but now his condition is worsening; we tried our best, but him passing away seems likely. We made this decision, and we accept the results and are willing to bear with the outcome. We know that the doctors did their best and thank them for it.

Table 5: Continued.

Subthemes	Codes	Quotes
		F7: Actually, to be honest, at first thought, you come to the hospital to cure people, right? But even after all efforts, if there is no way to recover from this disease, we have to accept that. This requires the doctor to clearly communicate with us and speak without being obscure so that we can prepare ourselves to bear any result.
Continuous service	"Shift change," "handover of special circumstances," and "understand details"	D1: We will do a detailed shift on the patient's condition, willingness of family members and communication problems. This ensures that doctors on shift or on weekends are getting consistent information as well.

Furthermore, the ability of healthcare providers to convey relevant theoretical knowledge to surrogates and patients' families in a simplified manner should be improved, which will reduce their work burden, improve the decision-making readiness of the family, and shorten the decision time.

This study identified several facilitators of SDM in the ICU setting. A previous study emphasized that ICU nurses should be involved in SDM [22]. Truglio et al. reported that owing to their rich clinical experience, ICU specialist nurses can contribute to SDM by guiding the surrogates with their decision-making process [23]. Nurses with longer and richer medical experience can better comprehend the psychological condition of patients and their families. Extending psychological support to patients' families helps SDM implementation by encouraging decision-makers to communicate and express their emotions. In routine care, caregivers should be empathetic, listen actively, and provide basic guidance with sufficient expertise in key areas of concern to the patient/family, including diet, complications, restraints, and skin-related issues. Supplementing verbal communication with reliable printed information leaflets or web-based decision aids is recommended. When surrogates are concerned about problems beyond the scope of nurses' expertise, the nursing staff should abridge the communication gap between physicians and surrogates to convey the perspective of surrogates to the physicians, thus optimizing the quality of nursing and improving the satisfaction of surrogates.

6. Study Limitations

Since the study includes a small sample size recruited from only one ICU of one hospital, the results may not be generalizable to all healthcare providers and surrogates. Nevertheless, the inclusion of different types of healthcare providers and surrogates offered a broad perspective on SDM, wherein we also identified consistent perspectives among the stakeholders regarding the perceived barriers and facilitators of SDM. Notwithstanding, additional (implementation) studies are needed to address these barriers and facilitators to improve the practice of SDM.

7. Conclusions

In the ICU, reaching treatment decisions is critical to proper medical management. It affects the patient's health outcomes and treatment experience. The necessary steps should be taken to implement SDM in a manner that is satisfactory to both agents and healthcare providers. Thirty participants (11 agents, 12 ICU physicians, and 7 ICU nurses) were interviewed. The three stakeholders showed different attitudes toward SDM. Based on this, we explored the attitudes of surrogates and health care providers toward SDM and identified the barriers and promoters of SDM in this population. In addition, this study also explored the different attitudes of the three stakeholders and found out various obstacles and promoting factors of SDM. It highlights the need to develop localised decision AIDS and to involve agents and nurses more in the decision-making process. Finally, we established the barriers and facilitators of SDM. The whole paper shows that the development of localised decision AIDS and greater involvement of agents and nurses in the decision-making process are integral to good treatment outcomes.

In the future, we hope to strengthen the attitudes and culture of both doctors and patients toward SDM. The medical side needs to accept the differences between the views of patients and medical staff and accept the questions of patients, so as to promote the SDM on the patient side and the public side. We also hope that people will understand that they are the owners of their own bodies and are responsible for their own health. It is not only a patient's right to express or ask questions to medical staff but also a duty to promote a positive medical environment through the joint efforts of both patients and doctors.

7.1. Relevance for Clinical Practice. SDM is currently in its infancy in ICU in China. To explore and clarify the barriers and facilitators affecting the implementation of SDM will help medical staff understand expectations of doctor-patient communication and decision-making from the perspective of surrogates and contribute to the promotion and application of SDM in clinical practice. This paper identifies barriers and facilitators of SDM in this population. In addition, the study identified various barriers and facilitators to SDM and highlighted the need to develop localized decision AIDS and involve agents and nurses more in the decision-making process. Finally, the barriers and facilitators of SDM are established. The paper shows that the development of localized decision AIDS and greater involvement of agents and nurses in the decision-making process are integral to good treatment outcomes.

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Retraction

Retracted: A Mixed Methods Investigation of the Prevalence and Influencing Factors of Compassion Fatigue among Midwives in Different Areas of China

Disease Markers

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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) Peer-review manipulation

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.

In addition, our investigation has also shown that one or more of the following human-subject reporting requirements has not been met in this article: ethical approval by an Institutional Review Board (IRB) committee or equivalent, patient/participant consent to participate, and/or agreement to publish patient/participant details (where relevant).

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.

References

[1] X. Liang, P. Yuan, X. Su et al., "A Mixed Methods Investigation of the Prevalence and Influencing Factors of Compassion Fatigue among Midwives in Different Areas of China," *Disease Markers*, vol. 2022, Article ID 1815417, 11 pages, 2022.

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Research Article

A Mixed Methods Investigation of the Prevalence and Influencing Factors of Compassion Fatigue among Midwives in Different Areas of China

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Objective. Exploring the influencing factors of compassion fatigue among midwives to prevent compassion fatigue from occurring and improve their mental health. *Methods*. A method integrating the quantitative research method and qualitative research method is used. For the quantitative research, a cross-sectional study was carried out. State-run hospitals from three economic areas in China were selected as investigation scope from June 2018 to May 2021. A total of 515 midwives were chosen randomly from three economic areas. SPSS 22.0 was used for data cleaning and statistical description and analysis. The influencing factors of compassion fatigue among midwives were analyzed by fitting these two-level logistic models. For qualitative research, purposive sampling and maximum variation strategy were used to select midwives with mild or above compassion fatigue in the questionnaire survey. Field study and interviews were used to collect data. *Results*. The results in the quantitative research showed that 515 valid questionnaires were received with 82.14% of midwives whose compassion fatigue were moderate or above. Multilevel statistical model analysis demonstrated that hospital level, children situation, area, working atmosphere, experiences of traumatic delivery, sleep quality, and social support level had impacts on the degree of midwives' compassion fatigue ($p < 0.05$). The result in the qualitative research showed that 34 midwives were interviewed, and 7 topic ideas were refined. *Conclusion*. Overall, the incidence of compassion fatigue among midwives is high. Risk factors influencing the degree of midwives' compassion fatigue include lower social support, disharmonious working atmosphere, toddler situation, huge workload, experiences of traumatic delivery, and poor quality of sleep.

1. Introduction

Medium and long term talent development plan of medicine and health 2011-2020 states that it is indispensable to improve team construction of midwives and create new policy, society, and working and living environment to develop talents [1]. Improve midwives' team construction is beneficial to maternal and fetal health and guarantees the high quality of care [2]. A slice of research [3, 4] has examined that traumatic stress influences mental health of midwives and further affects team construction, wherein the most common traumatic stress is traumatic delivery. 78.7% to 84% of midwives experienced at least one traumatic delivery in their works. Traumatic delivery is defined as a series of events that introduce threatening injury or even the risk of death to fetus and puerpera during labor or after a few hours postpartum, such as stillbirth, shoulder dystocia, three-degree perineal laceration, and postpartum hemorrhage.

Furthermore, traumatic delivery brings psychological trauma to puerpera and their families and causes traumatic stress reactions among midwives [5–8]. With the opening of two-child policy and the development of birth attendance in China, people put forward more and more demands with the ability of midwives, meanwhile, the workload and work strength of midwives are soaring. Midwives should not only be professional but also take responsibility for caring mental health of puerperae. Due to high risks and heavy workloads, midwives always encounter situations full of stressors during clinical works, which increases the incidence of compassion fatigue [9]. It not only affects the physical and mental health of midwives but also affects the quality of midwifery technology and team building. Their working status, mood, and attitude will also directly affect the physical and mental health and safety of pregnant women. At present, the research on compassion fatigue of midwives abroad is relatively mature, and it has gradually expanded to the study of the connotation and influencing factors of compassion fatigue, intervention implementation, and effect evaluation. In China, only cross-sectional research on midwives' job burnout is conducted, while job burnout is one of the three factors of compassion fatigue. At the same time, due to cultural differences in China and abroad and different hospital management policies in my country, such as different employment forms, leadership styles, and hospital levels, it may be a risk factor for midwives to reduce compassion fatigue. Therefore, it is necessary to analyze the status quo of compassion fatigue of midwives in our country and its influencing factors.

Adams et al.' research [10] states that low social support can worse compassion fatigue among midwives, accordingly, deeply understanding the influencing factors of social support can provide a basis for increase the level of social support. Meanwhile, because of a vast territory and unequal distribution of medical resources in China, influences of regional disparities on midwives' compassion fatigue are worthy of study. In addition, the assessment of physical and mental health of midwives should not only focus on their status but also pour attention into their experiences, where in the diversity of experiences is mostly mutual communication based. Thus, explanatory sequential mixed methods design was used to research midwives from different hospitals in different provinces. Multilevel samples were representative, which can verify and supplement quantitative research and improve excessive dependence on qualities of researchers in qualitative research, in order to make up for the lack of in-depth and dynamic emotional research on the research objects, the current research mostly uses quantitative research.

2. Methods

2.1. Research Questions. Four specific research questions were asked: (1) are there any differences among midwives from different hospitals in different areas in terms of the degree of compassion fatigue? (2) What are influencing factors of compassion fatigue among midwives? (3) Are midwives more serious than nurses from other departments in terms of the degree of compassion fatigue? (4) How to integrate quantitative research with qualitative research effectively to make a clear and accurate analysis of influencing factors of compassion fatigue among midwives?

2.2. Design. This study used explanatory sequential mixed methods design, including two stages. The first stage was collecting quantitative data and then making analysis. Qualitative research [11] was conducted by using the results obtained from the first stage, followed by explaining research results. Cross-sectional study was used in quantitative research. Qualitative research used field study to collect data, including field observation, fieldwork notes, and semistructured and in-depth interviews.

2.3. Participants and procedure. Convenient sampling was used to select public hospitals from three economic areas in eastern, central, and western China from June 2018 to May 2021, followed by randomly choosing four provinces from eastern, central, and western China, respectively, in the range of 35 provinces and municipalities in these three economic areas. Once 12 provinces are obtained, 57 hospitals were chosen from secondary, tertiary, and specialized hospitals in selected provinces by using convenient sampling. Then, based on inclusion and exclusion criteria, purposive sampling was used to choose participants ($n = 515$). The inclusion criteria are (1) obtained a Practicing Nurse Certificate and certificate of maternal and infant health care from China, (2) currently works in midwifery, and (3) the working experience is more than 1 year. The exclusion criteria are off-duty midwives because of studying abroad, sick and maternity leave, etc.

Qualitative research used purposive sampling to choose midwives with mild or above compassion fatigue in the questionnaire survey from secondary, tertiary, and specialized hospitals in 6 provinces in quantitative research. To make samples more representative, principle of maximum differentiation was used, to the greatest extent, to select midwives of different ages, titles, hospital levels, areas, and compassion fatigue degree ($n = 34$).

2.4. Research tools

(1) *General Information Questionnaire.* Questionnaires were self-designed, followed by revising the contents by a panel of experts comprised of 5 associate high or above obstetrics nursing management experts. This questionnaire comprised fundamental information and working environment, the content validity of this questionnaire is 0.92 and Cronbach's α is 0.79

(2) *Compassion Fatigue Scale.* This scale was developed by Figley and Stamm [12, 13] in 1980s and was used to quantitatively measure compassion fatigue. Each dimension includes 10 items and 30 items in total. Likert 5-class scoring method is used, where 0 indicated strongly unmatched, and 5 indicated strongly matched. The critical values of three dimensions are <37, >27, and >17, respectively. Cronbach's α

of three dimensions are 0.88, 0.75, and 0.81 separately

(3) *Social Support Scale*. This scale was used to measure the degree of social support that an individual receives [13]. This scale includes three dimensions, objective support (three items), subjective support (four items), and support availability (three items). In this scale, low, medium, and high social support are defined as less than score 33, between score 33 and 45, more than score 45, respectively. The test-retest reliability of this scale is 0.92, and the Cronbach's α of three dimensions are between 0.89 and 0.94

(4) *Interview Outlines*. The questions asked are the following: (1) are there any negative emotions in your work? What are the causes? (2) Does working environment or the style of leader affect your working status? (3) Are there some occasions when the womb is in a crisis caused by adverse events in your work? (4) What are your feelings when faced with pains of puerperae or other appeals in your work? (5) As a midwife, what are your opinions on the supports from family, work, and society? To what extent of these supports? (6) How do you deal with the relationship between family and work? (7) Do you ever desire to quit your job or transfer to other departments during working? (If so, would you mind telling the reasons?)

2.5. Data collection methods. Data collection methods in this study included field questionnaire survey and online questionnaire survey.

[1] *Field questionnaire survey*. Field questionnaire survey was in the charge of a researcher who carried out field investigations to surrounding provinces and cities (Hubei, Henan, and Anhui province) of the researcher's area. By the statistics, there were 146 questionnaires issued and 144 were effectively received with effective recovery of 98.63%.

[2] *Online questionnaire survey*. Online questionnaire investigation was made in other provinces and municipalities, and it is indispensable to recruit liaisons from local hospitals. Liaisons should be medical workers and were required to have research basis and obtain at least bachelor's degree. In addition, video training, which should identify the purposes and significance of this research and filling details of scales, was provided for liaisons. Every liaison built a WeChat questionnaire group for their own hospital, and the group administrators would include the researcher, liaison, and people in charge of departments, and group members were research objects. Department heads took responsibility to arrange filling time and supervise the whole process. Liaisons were in charge of distributing the QR code of questionnaire and explaining the investigation purposes, contents, and notice. There were 376 questionnaires issued and 371 were effectively received with effective recovery of 98.67%.

Qualitative researches included in this study are field study and interviews.

[1] *Field Study*. Since field study for in-depth research were feasible in hospitals of Henan, Hubei, and Chongqing provinces, typical and representative objects were selected to conduct on-site and in-depth interviews.

[2] *Interviews*. As for midwives of other provinces, due to the infeasibility of field work, research objects would be chosen according to maximum differences and representativeness to conduct visual interviews, which offset the small sample size and limited representativeness of field study and avoid subjective bias. Under the nursing department's leadership or recommendation, researcher, as a trainee of midwife, participated in the field observation training and studied delivery rooms' working procedures, techniques and regulations systematically. From June 5, 2017 to January 10, 2020, researcher observes the working status of the midwives, and then built trust relationships with them, followed by full participation observation. Besides collecting data by observing and listening, researcher should also record and edit all data observed and then transcribe these data within 24 hours. Appointments with participants who accord with inclusion criteria should be made in advance. Based on the will of the researcher, interview spots could be private, quiet, and comfortable. Every interview would last 30 to 60 minutes. When face-to-face communications were impossible, WeChat video interviews were used. Before the WeChat video interview, the researcher could gain the trust of participants by chatting on WeChat for 10 to 20 days and understand their working and living status in the following 2 to 4 months. The researcher uses WeChat Video to build a face-to-face communication if the interviewees approve. To keep the internet connection available and high video quality, both interviewees and researcher were suggested to choose private and peaceful spots with excellent internet connection.

2.6. Data Analysis. EpiData 3.1 was used to build database, and the data were parallel inputted by two individuals, followed by consistency checks. In the data processing and statistical analysis using SPSS 22.0, the measurement data used mean and standard deviation and the count data used frequency and percentage. In terms of single factor analysis, the categorical data used chi-square test and the ranked data used nonparameter Kruskal–Wallis test. Considering that data had a hierarchical structure of hospital and individual, MLwiN 2.30 package was used to analyze the influencing factors of midwives' compassion fatigue by multilevel statistical models. Individuals and hospitals were defined as level 1 and level 2, respectively, followed by fitting two-level logistic models.

Recording and notes need be transcribed within 24 hours after interviews. Then, the transcribed contents should be checked to ensure that all information was true and correct. Content analysis method was adopted in descriptive qualitative research [14], when the subjects were fully determined, interviewer and interviewees should work together to carry on checking process to guarantee the validity of interpretation and data saturation.

3. Results

3.1. General information comparison. In this study, 515 midwives from 57 hospitals are all females, whose ages are between 23 and 43 (29.84 ± 4.92). Among these midwives, 225 (43.8%) have 1-5 years of working experience, 159 (30.8%) have 6-10 years of working experience, 78 (15.1%) have 11-15 years of working experience, and 53 (10.3%) have more than 15-year experience; 5 midwives (0.9%) only have technical secondary school qualifications, 136 (26.6%) only have college degrees, 370 (71.7%) have bachelor's degrees, and 4 (0.8%) have master's degrees. The sampling situation of investigated hospitals is shown in Table 1.

3.2. Single Factor Analysis Results of Midwives' Compassion Fatigue. Single factor analysis results (Table 2) demonstrate that age, marriage situation, hospital level, children situation, numbers of experiences of traumatic delivery, area, working conditions, workload, working environment, level of social support all impact the degree of midwives' compassion fatigue ($P < 0.05$).

3.3. Multilevel Statistical Models Analysis of Midwives' Compassion Fatigue. Individuals and hospitals were defined as level 1 and level 2, respectively, followed by fitting two-level logistic models. Results manifest that the variance of level 2 is 0.926 ($P < 0.05$), which means clustering of hospital level exists and the hierarchical structure is not neglected, so multilevel statistical models analysis should be adopted, as is shown in Table 3. Furthermore, some meaningful impact factors from single factor analysis had been introduced into two-level logistic regression models, and analysis had been made for existed models, where unordered categorical variables (hospital, marriage situation, and area) were introduced as dummy variables, and ordered categorical variables were introduced as grouping linear variables and dummy variables, respectively, followed by fitting model 1 and model 2. Ultimately, all ordered categorical variables were introduced as dummy variables by judging whether these two models had statistical significance and linear trend. Assignment method of independent variables is shown in Table 4. Results demonstrate that the level of hospital, area, sleep quality, numbers of experiences of traumatic delivery, children situation, working environment, and the level of social support are all the impact factors of midwives' compassion fatigue ($P < 0.05$), as is shown in Table 5.

3.4. Qualitative research. In this study, 34 female midwives, whose mean age was 32.32 ± 4.57, more details are shown in Table 6, were interviewed. The degree of compassion fatigue of them were all mild or above. This research conducted 34 semistructured interviews and transcribed 210,000 words, and then analyzed these transcribed data and field notes to refine themes,, a total of 7 themes, and 24 subthemes. In the date analysis results, field notes were in italics.

3.4.1. Theme 1: Excessive Workloads Lead to Negative Emotions. Painful: "The working hours are too long for both day shifts and night shifts and there is no break when working. The whole process is miserable so that I am in no mood to relax myself." (eyes moist) (ID 2).

Exhausted: *Staying up all night with midwife teacher is extremely common. Keeping a good state at every moment is crucial, because there are many deliveries in the night shifts and puerperae are easily to become exhausted on the night.*

Nervous: "As a new midwife, I feel nervous with increasing deliveries in recent two years. I have ever thought about quitting because I am worried about making mistakes under large workloads. I am extremely anxious and desire to cry sometimes" (choked up) (M 4).

3.4.2. Theme 2: Incomplete Social Support System. Misunderstandings Exist: "What disappoints us is families of puerperae buy gifts to thank for doctors and neglect our efforts after delivery. We do not care about gifts and what we need is recognition (eyes moist)." (ID 29).

Insufficient Material Needs Support: "I am working as a midwife for 30 years. I bring in 3000 CNY a month, which is not enough to support my family. We take more risks but obtain less. It would be great if basic hospitals could raise salaries." (ID 12).

Desire to Receive Attention: Some midwives were delighted to discuss how to prepare for Nurses Day (May 12th). However, after a while, they were told that there was no need for midwives to prepare programs but nurses from obstetrics department can. On hearing this news, all people felt upset without saying a single word.

Imbalanced Social Support: "Workers in western hospitals lack systematic study of midwifery for many years. Though I am assiduous and work for many years, I still see the large gap between us and provincial or municipal hospitals when I take part in provincial or municipal trainings. Many colleagues of mine have never ever left home." (ID 30).

3.4.3. Theme 3: High Level of Psychological Flexibility. Head nurse praised a midwife in one regular meeting, who gets divorced but always keeps positive. She needs to send her school-age kid to school by herself regardless of the weather. Instead of complaining the unfair life, she always helps others and participates in charity activities. Meanwhile, when she was praised, she also appreciated the understanding of other colleagues.

Positive: "Perhaps due to young age, I am positive to everything. Each time when I see the newborn in delivery rooms, I feel delighted and confident." (ID 7).

Mental Self-Adjustment: "The ability to self-adjustment is crucial in working. Some negative emotions and things will fade with time, so I do not think too much about that and feel satisfied." (ID 17).

Positive Mental Feedback: "I am working for long and have delivered many newborns. Sometimes when I am shopping or at supermarket, some individuals recognize me and say, 'it is you who delivered our children', from which I can feel their gratitude. Though it is just a sentence, I still feel delighted and will more assiduous in work." (ID 5).

3.4.4. Theme 4: Experiences of Traumatic Delivery. Numbers of Traumatic Delivery: "I experienced many traumatic deliveries in my 15-year career, which leaves me scarred. Sometimes I feel extremely worried and desire to go to other departments." (ID 8).

Table 1: Numbers of investigated hospitals.

Area/Province	Hospital(numbers, $n = 57$)			Midwives [Number (percentage %)]
	Secondary	Tertiary	Specialized	
Eastern area				170 (33.01)
Hebei	2	2	1	40 (7.77)
Jiangsu	1	2	1	45 (8.74)
Guangdong	2	2	2	43 (8.35)
Shandong	1	2	1	42 (8.15)
Central area				170 (33.01)
Hubei	2	2	1	47 (9.13)
Henan	2	2	1	46 (8.93)
Jiangxi	1	2	1	40 (7.77)
Anhui	2	2	1	37 (7.18)
Western area				175 (33.98)
Gansu	2	2	1	49 (9.51)
Qinghai	2	1	1	41 (7.96)
Chongqing	2	2	1	45(8.74)
Guizhou	2	2	1	40 (7.77)

Severity of Traumatic Delivery: "Once, there was a puerpera with amniotic fluid embolism (AFE) and we tried our best but failed. I witnessed the death of the woman, which made me extremely painful and struggling for a long time. Even now I still scarcely dare think of that matter." (ID 27).

Inappropriate Handling of Superior: "Once we failed in rescuing a premature baby, the families were very angry and wanted answers. A leader, who did not understand midwifery, rebuked us and tried to find who to blame, which left us with large psychological scars." (ID 15).

Negative Handling of Superior: When families make troubles, the head nurse directly hides away. Some midwives are scolded by the families with tears and they do not know how to do but only apologies, which makes worse. They hope that the superior can come to help to deal with the problem. However, instead of leaders, security personnel come only to persuade the family to leave. These midwives know that this matter cannot be handled without the appearance of leaders.

3.4.5. Theme 5: Large Physical Workload. Unwell Symptom: "We should be always ready for working at lunchtime of day shifts. We worry about the situation of puerperae, so we are too nervous to have lunch, which can cause dyspepsia. In addition, I have severe scapulohumeral periarthritis so that I cannot feel the breeze and be too tired." (ID 1).

Harmful Stimulation: "When there is no pain-free delivery, sometimes puerperae shout loudly, which is a kind of harmful stimulation. In the meantime, we will doubt that whether contractions or any other unwell symptoms occur, which makes us worried and depressed." (ID 9).

Overdo the Sympathy: "Once we induced a puerpera because the 8-month baby had hydrothorax and hydroabdomen. Due to sympathy, we did the natural labour. Unfortunately, the puerpera died because of amniotic fluid embolism. Actually, as a midwife, overdoing the sympathy may hurt puerperae even more. Investing too much emotion may impede making a right decision." (ID 33).

3.4.6. Theme 6: Poor Working Environment. Disharmony Relationships with Colleagues: "Instead of workloads, disharmony relationships with colleagues and leaders can drive people crazy. If you cannot get along well with your colleagues and leaders, you will suffer from work and feel frustrated." (ID 14).

Unreasonable management system: ID 4 said that in their department, they have no say in many matters and anything will be decided by our leaders. She thinks this research is valuable, and they can express their hearts.

Leader Lack Responsibilities: "Our leader does not have a strong sense of responsibility. When medical disputes occur, the leader will pass the buck on us. I feel frustrated and lack enthusiasm for working." (ID 22).

Lack the Cooperation between Doctors and Midwives: "We do not have enough communications with doctors. If there are differences between their knowledge and our guidelines, we cannot work well with each other and may have disagreements." (ID 28).

3.4.7. Theme 7: Unbalance Between Work and Family. Owe to Families: "We are much busier than usual during festivals and I have already been on duty on New Year's Eve for 10 years. My dad always complains that I have not enough time to spend with them. I feel guilty and owe them so much." (ID 31).

Self-sacrifice: "I desire to have a second child because of the two-child policy. However, I chose to miscarry due to large pressure and workloads. I was suffering from making this choice for a long time. I would say I give up many things for my work and feel helpless (silent tears)." (ID 34).

Helpless: "My family does not understand me and think it is unfair for me to do such a busy work but earn the less money. When I go to work after maternity leave, they go to the hospital to defend against my situation, which has become a joke in the eyes of my colleagues. I scold myself for my powerless and feel overwhelmed." (ID 22).

Table 2: Single factor analysis of compassion fatigue among midwives.

Project	Degree of compassion fatigue		Statistics	P value
	None and mild	Moderate and above		
Level of hospital			12.040[1]	0.002
Secondary	15 (8.98)	152 (91.02)		
Tertiary	29 (16.86)	143 (83.14)		
Specialized	48 (27.27)	128 (72.73)		
Area			18.860[1]	< 0.001
Eastern	61 (23.78)	129 (76.22)		
Central	38 (21.25)	132 (78.75)		
Western	15 (8.58)	160 (91.42)		
Age			32.601[2]	< 0.001
20~	35 (38.89)	55 (61.11)		
2 6~	26 (13.54)	166 (86.46)		
3 1 ~	15 (10.71)	125 (89.28)		
> 3 5	15 (16.13)	78 (83.87)		
Marriage situation				
Unmarried	47 (34.06)	91 (65.94)	45.560[1]	< 0.001
Married	44 (12.72)	302 (87.28)		
Divorced	2 (6.45)	29 (93.55)		
Sleep quality			24.760[2]	< 0.001
Normal	34 (31.78)	73 (68.22)		
Occasional insomnia	37 (16.89)	182 (83.11)		
Frequent insomnia	12 (7.95)	139 (92.05)		
Children situation			59.646[2]	< 0.001
None	53 (35.57)	96 (66.43)		
Infant	18 (11.18)	143 (88.81)		
School-age	6 (5.04)	113 (94.96)		
Junior school and above	17 (19.77)	69 (80.23)		
Experiences of traumatic delivery			76.138[2]	< 0.001
0	29 (60.42)	19 (39.58)		
1~	14 (11.20)	111 (88.80)		
3~	17 (11.41)	132 (88.59)		
> 5	13 (6.74)	180 (93.26)		
Job satisfaction			44.039[2]	< 0.001
Very satisfied	4 (40.00)	6 (60.00)		
Satisfied	47 (37.90)	77 (62.10)		
Ordinary	29 (10.43)	249 (89.57)		
Very unsatisfied	6 (5.83)	97 (94.17)		
Whether workload is too large			13.656[2]	0.004
Yes	36 (14.46)	213 (88.54)		
Ordinary	49 (20.08)	195 (79.92)		
No	3 (13.64)	19 (86.36)		
Whether to like work environment			20.753[2]	< 0.001
Yes	47 (27.81)	122 (72.19)		
Ordinary	32 (12.17)	231 (87.83)		
No	4 (4.82)	79 (95.18)		
Social support level			113.154[2]	< 0.001
Low	12 (7.36)	151 (92.64)		
Medium	28 (9.89)	255 (90.11)		
High	43 (62.31)	26 (37.69)		

Note. 1: $\chi2$ value; 2: $\chi2$ value (Kruskal–Wallis).

Table 3: Zero-level analysis of two-level variance components.

Parameter	Estimate	Standard error	P value
Fixed effect			
Intercept	1.7768	0.1722	< 0.0001
Random effect			
Level 2 variance	0.6895	0.2931	0.0093
Level 1	1		

4. Discussion

This research demonstrated that compassion satisfaction scored (32.64 ± 6.47), job burnout scored (27.89 ± 5.01), and secondary traumatic stress scored (26.31 ± 5.70). The scores all exceeded their critical values. The scores of all dimensions of compassion fatigue were higher than those of the mental health nurses and the oncology nurses. The compassion fatigue scores of midwives were moderate or above. The incidence is higher than that of nurses in general clinical departments studied [15–17]. The incidence of mild or above compassion fatigue among midwives was higher than nurses from common departments [17]. Most puerperae and their families lack the psychological adaptation stage for some emergencies in delivery rooms. Thus, when emergencies occur, it will be difficult for puerperae and their families to accept, and they will have extreme emotions or behaviors. These emotions, behaviors, or the matter itself will leave scares on midwives and impact their careers [18]. At the same time, when observing labor, the midwife not only bears the demands and groans caused by the mother's pain, but this kind of bad sound stimulation makes the midwife bear the greater mental and psychological pressure in addition to the safety of pregnancy and fetal life. In Rice's study [19], 35% of midwives had moderate or above compassion fatigue, which is different from the 82.13% of moderate or above compassion fatigue in this study, which may be compared with the number of births after the opening of the second child policy in China. As high-risk and elderly mothers increase, midwives need to undertake high-level and continuous maternal and child health prenatal, mid- and postnatal care services, which put midwives in stress and high-load, high-risk work conditions, also probably, the number of midwives per 1,000 population in our country is 0.05, which is much lower than that of developed countries and some developing countries. The shortage of human resources allocation on the one hand, must meet the needs of new midwifery training and learning needs for new midwifery technology and Doula services, and on the other hand, it must meet the human resource needs of the development of Doula midwifery services, which is related to the heavy workload [20].

Muliira [21] indicates in his study that midwives in the deprived areas or basic hospitals are more prone to have compassion fatigue because of poor medical environment, low wages, and the lack of social support. This research arrived at the same conclusion. Secondary and western hospitals have lower resource support, poorer medical conditions, and lower wages than other hospitals in China. Especially in western areas, the requirement of quantity of midwives is higher and the level of care for serious diseases is lower. With the demanding requirements of specialized abilities for midwives, they still cannot have sufficient chances to participate in training outside [22]. In China, obstetrics resources mainly focus on areas with a large population, leading to the unbalanced distribution of health resources [23]. This study also demonstrated that the level of midwives' compassion fatigue in tertiary hospitals was higher than specialized hospitals. The possible reasons could be that the numbers of older puerperae increases because of the childbearing policy and tertiary hospitals conduct more rescue work of serious diseases with taking more risks. Combined with the policy, it is crucial to build the talent group for grassroots health care and establish the mechanism of division and cooperation of medical institutions in integrated health care system [24]. Meanwhile, to advance the balanced development of different classes of hospitals in different areas, tertiary hospitals are encouraged to develop close relationship with secondary and basic hospitals and assist to optimize medical resources. In addition, in this study, there was a negative correlation between social support level and compassion fatigue level. Sadie [25] has examined that supports from family, friends, and organization is crucial for midwives. Lacking supports from colleagues and leaders can make midwives lack the sense of belonging [26], thus increasing repressed emotions of midwives. Some research state that insufficient social support can increase the incidence of compassion fatigue of midwives [27]. The low objective support in this study indicates that the support from social groups, organizations, family, and friends to midwives is low. The lack of support from colleagues, leaders, and teams at work, or lack of recognition and attention will make midwives feel that the working atmosphere is not harmonious, will make midwives feel double pressure from work and life, and easily cause midwives to empathize and fatigue. The low use of support means that the individual cannot perceive all aspects of support. On the one hand, it is due to the low objective support. On the other hand, it shows that the individual cannot make good use of the objective conditions brought about by objective support and cannot recognize objective support. The material and spiritual needs brought about, and the use of support is closely related to the job burnout of midwives, which also shows that individuals cannot perceive and use the support from external organizations and society and there will be numbness and burnout at work more serious.

In this research, 66.41% of midwives experienced at least three traumatic deliveries. The more traumatic deliveries they experienced, the more serious their compassion fatigue level would be. In other ways, more traumatic deliveries can make midwives lack confidence of their skills and abilities, thus producing negative emotions and inducing compassion fatigue [2]. Organizing and rationally handling childbirth traumatic events is the greatest traumatic psychological support for midwives. According to Julia's systematic reviews [25], experiencing traumatic deliveries will increase the risk of traumatic stress reactions, further forming a series of compassion fatigue symptoms such as "Sympathy price",

Table 4: Independent variables assignment table.

Variables	Value
Compassion fatigue	None and mild = 0, Moderate and above = 1
Hospital Level	Specialized hospital ($Z1 = 0$, $Z2 = 0$), Secondary ($Z1 = 1$, $Z2 = 0$), Tertiary ($Z1 = 0$, $Z2 = 1$)
Area	Eastern area ($Z1 = 0$, $Z2 = 0$), Central area ($Z1 = 1$, $Z2 = 0$), Western area ($Z1 = 0$, $Z2 = 1$)
Age	20~ ($Z1 = 0$, $Z2 = 0$, $Z3 = 0$), 26~ ($Z1 = 1$, $Z2 = 0$, $Z3 = 0$), 31~ ($Z_1 = 0$, $Z2 = 1$, $Z3 = 0$), >35 ($Z1 = 0$, $Z2 = 0$, $Z3 = 1$)
Marriage situation	Unmarried ($Z1 = 0$, $Z2 = 0$), Married ($Z1 = 1$, $Z2 = 0$), Divorced ($Z1 = 0$, $Z2 = 1$)
Sleep quality	Normal ($Z1 = 0$, $Z2 = 0$), Occasional insomnia ($Z1 = 1$, $Z2 = 0$), Frequent insomnia ($Z1 = 0$, $Z2 = 1$)
Children situation	None ($Z1 = 0$, $Z2 = 0$, $Z3 = 0$), Infant ($Z1 = 1$, $Z2 = 0$, $Z3 = 0$), School-age ($Z1 = 0$, $Z2 = 1$, $Z3 = 0$), Junior school and above ($Z1 = 0$, $Z2 = 0$, $Z3 = 1$)
Experiences of traumatic delivery	0 ($Z1 = 0$, $Z2 = 0$, $Z3 = 0$), 1~2 ($Z1 = 1$, $Z2 = 0$, $Z3 = 0$), 3~5 ($Z1 = 0$, $Z2 = 1$, $Z3 = 0$), >5 ($Z1 = 0$, $Z2 = 0$, $Z3 = 1$)
Job satisfaction	Very satisfied ($Z1 = 0$, $Z2 = 0$, $Z3 = 0$), Satisfied ($Z1 = 1$, $Z2 = 0$, $Z3 = 0$), Ordinary ($Z1 = 0$, $Z2 = 1$, $Z3 = 0$), Very unsatisfied ($Z1 = 0$, $Z2 = 0$, $Z3 = 1$)
Whether workload is too large	Yes ($Z1 = 0$, $Z2 = 0$), Medium ($Z1 = 1$, $Z2 = 0$), No ($Z1 = 0$, $Z2 = 1$)
Whether to like the working environment	Yes ($Z1 = 0$, $Z2 = 0$), Medium ($Z1 = 1$, $Z2 = 0$), No ($Z1 = 0$, $Z2 = 1$)
Social support level	Low ($Z1 = 0$, $Z2 = 0$), Medium ($Z1 = 1$, $Z2 = 0$), High ($Z1 = 0$, $Z2 = 1$)

Table 5: Multilevel statistical models analysis results of impact factors of midwives' compassion fatigue.

Independent variables	Estimated value	Standard error	P value	OR Value (95% CI)
Intercept	3.2069	1.3623	0.009	—
Level 2 (Hospital)				
Hospital level (Specialized)				1
Secondary	-0.2361	1.2622	0.8517	0.790
Tertiary	-4.4947	1.1901	0.0002	0.011
Area (East)				1
Central	-1.4854	1.0147	0.1440	0.226
Western	-3.3545	0.8654	0.0001	0.035
Level 1 (Individual)				
Sleep quality (normal)				1
Occasional insomnia	-0.01376	0.9014	0.9878	0.986
Frequent insomnia	0.3906	1.4038	0.7809	1.478
Children situation (None)	0.1325	1.4651	0.9280	1.142
Infant				1
School-age	1.1807	1.1457	0.3033	3.257
Junior school and above	2.5925	2.2225	0.2441	13.363
Experiences of traumatic delivery (0)	0	.	.	1
1~2	1.4194	1.0684	0.1847	1.805
3~5	1.2981	1.5081	0.3899	2.708
>5	-0.576	1.2398	0.6425	1
Whether to like working environment (Yes)	0	.	.	4.134
Medium	0.5903	0.6793	0.3853	3.662
No	0.9961	0.8083	0.2185	0.562
Social support level (Low)	0	.	.	1
Medium	1.7773	0.9261	0.0556	5.914
High	1.4653	0.9415	0.1203	4.329

Table 6: Basic information of 34 midwives.

Coding	Interview method	Age	Title grade	Marriage situation	Children situation	years	Hospital level	Province	ETD	CF degree
M1	Video	29	Junior	Married	School-age	3	Secondary	Shandong	3	Moderate
M2	Video	34	Junior	Married	Primary school	7	Tertiary	Shandong	> 5	Moderate
M3	Face-to-face	29	Junior	Married	School-age	6	Tertiary	Shandong	3	Moderate
M4	Video	27	Junior	unmarried	None	4	Specialized	Shandong	4	Moderate
M5	Video	29	Junior	Married	None	6	Secondary	Shandong	3	Severe
M6	Face-to-face	39	Middle	Married	Junior school	17	Tertiary	Hebei	> 5	Moderate
M7	Video	26	Junior	unmarried	None	2	Tertiary	Hebei	2	Moderate
M8	Video	35	Junior	Married	Junior school	15	Secondary	Hebei	> 5	Moderate
M9	Face-to-face	34	Junior	Married	Primary school	12	Specialized	Hebei	> 5	Moderate
M10	Video	28	Junior	Married	School-age	5	Secondary	Hebei	3	Severe
M11	Face-to-face	37	Junior	Divorced	Primary school	27	Secondary	Henan	> 5	Mild
M12	Face-to-face	38	Middle	Married	University	28	Secondary	Henan	> 5	Moderate
M13	Face-to-face	32	Middle	Married	School-age	10	Specialized	Henan	> 5	Moderate
M14	Face-to-face	34	Junior	Married	School-age	12	Secondary	Henan	4	Moderate
M15	Face-to-face	30	Junior	Married	School-age	6	Tertiary	Henan	3	Moderate
M16	Face-to-face	30	Junior	Married	School-age	8	Tertiary	Henan	4	Moderate
M17	Face-to-face	32	Junior	Married	Primary school	4	Tertiary	Hubei	> 5	Moderate
M18	Face-to-face	45	Middle	Married	University	27	Specialized	Hubei	> 5	Moderate
M19	Face-to-face	28	Junior	unmarried	None	4	Secondary	Hubei	4	Severe
M20	Video	39	Middle	Married	University	19	Tertiary	Hubei	> 5	Severe
M21	Video	34	Junior	Married	Primary school	12	Tertiary	Hubei	> 5	Moderate
M22	Face-to-face	33	Junior	Married	School-age	9	Secondary	Hubei	4	Moderate
M23	Face-to-face	34	Middle	Married	Primary school	5	Tertiary	Chongqing	4	Severe
M24	Face-to-face	31	Middle	Married	Primary school	10	Secondary	Chongqing	3	Moderate
M25	Face-to-face	31	Junior	Married	School-age	9	Tertiary	Chongqing	3	Moderate
M26	Face-to-face	26	Junior	unmarried	None	5	Specialized	Chongqing	4	Moderate
M27	Face-to-face	29	Junior	Married	School-age	5	Secondary	Chongqing	3	Moderate
M28	Face-to-face	28	Junior	Married	School-age	5	Secondary	Chongqing	4	Moderate
M29	Video	29	Junior	Married	Primary school	7	Tertiary	Gansu	> 5	Moderate
M30	Video	33	Middle	Married	Junior school	12	Tertiary	Gansu	> 5	Moderate
M31	Video	37	Junior	Married	Junior High school	27	Secondary	Gansu	> 5	Moderate
M32	Face-to-face	24	Junior	unmarried	None	2	Tertiary	Gansu	2	Moderate
M33	Video	34	Junior	Married	Primary school	10	Secondary	Gansu	3	Moderate
M34	Video	29	Junior	Married	School-age	5	Specialized	Gansu	2	Severe

Note: EBT(Experienced birth trauma).

.that reaches a consensus with this study. Traumatic delivery can not only bring pains and trauma to midwives but also make them feel the lack of capacity for compassion increasingly, which is the primary reason of compassion fatigue [28]. When adverse childbirth events occur, puerperae and families are formidable to accept, and conflicts, or even violence, will happen. Therefore, what leaders will do to cope with this situation will impact midwives. In this research, some leaders only focus on comforting puerperae and their families and hold the midwives accountable. Whereas, some midwives who are mentally weak will get into extreme panic and anxiety if the hospital cannot handle this problem positively. Instead, there are some organizations abroad providing psychological supports and helps to those who experience traumatic deliveries, so as to ensure that they can better devote into work [29].

Pierce [30] argues that due to passive work postures and large workloads, 40% of midwives have some predictable diseases, such as lumbago caused by lumbar muscle strain and lower urinary tract symptoms (LUTS) caused by delayed micturition and stressed obesity. This contributes a lot to the increasing rate of job changes of midwives. In this study, poor sleep quality is the impact factor of compassion fatigue, and sleep disorder is one of the physical symptoms of compassion fatigue. On the one hand, some predictable diseases from working can lead to insomnia; on the other hand, puerperae always release the highest levels of oxytocin and melatonin in the night so that the most of deliveries happen in the night. This make midwives work overtime in night shifts and thus influences their physiological sleep cycle [31]. Meanwhile, because of the particularity of working environment and large workloads, midwives may have a series of unwell symptoms, such as dyspepsia, shoulder pains, palpitation, and nervousness. Such a situation can reduce the motivation of midwives and increase their physical and mental loads. Consequently, it is crucial to pour attention to both mental and physical health of midwives, so as to conduct the human-based management.

5. Conclusion

This research covers 3 economic areas, 12 provinces, and 57 different levels of public hospitals, thus the results are representative. This study only concentrates on midwives who are still occupied in midwifery, however, the staff turnover of midwifery keeps a high level in China. Future study can focus on resigned personnel or transferees to other departments to optimize the construction of midwife team. Meanwhile, workloads, wages, and working environment are all analyzed from the subjective point of view of midwives. It is worthwhile, make them more quantifiable in future research to make data more objective.

Data Availability

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

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Xin Liang, Ping Yuan, Xingyan Su, and Yuanyuan Xing contributed equally to this work.

References

[1] Ministry of Health, China, "Medical and Health Talent Development Plan (2011-2020) [EB/OL]," (2011-04-28)[2019-10-20], http://www.gov.cn/zwgk/2011-04/28/content_1854246.htm.

[2] J. Leinweber, D. K. Creedy, H. Rowe, and J. Gamble, "A socio-ecological model of posttraumatic stress among Australian midwives," *Midwifery*, vol. 45, pp. 7–13, 2017.

[3] C. Favrod, L. Jan du Chêne, C. Martin Soelch et al., "Mental health symptoms and work-related stressors in hospital midwives and NICU nurses: A mixed methods study," *Frontiers in Psychiatry*, vol. 9, p. 364, 2018.

[4] C. T. Beck and R. K. Gable, "A mixed methods study of secondary traumatic stress in labor and delivery nurses," *Journal of Obstetric, Gynecologic, and Neonatal Nursing*, vol. 41, no. 6, pp. 747–760, 2012.

[5] L. Xin, G. Zumei, C. Lan, Y. Jingmin, and H. Rong, "Research progress on the impact of traumatic childbirth events on empathy fatigue of midwives," *Nursing Research*, vol. 34, no. 3, pp. 447–451, 2020.

[6] S. Hamilton, V. Tran, and J. Jamieson, "Compassion fatigue in emergency medicine: the cost of caring," *Emergency Medicine Australasia*, vol. 28, no. 1, pp. 100–103, 2016.

[7] R. Elmir, J. Pangas, H. Dahlen, and V. Schmied, "A meta-ethnographic synthesis of midwives' and nurses' experiences of adverse labour and birth events," *Journal of Clinical Nursing*, vol. 26, no. 23-24, pp. 4184–4200, 2017.

[8] C. Chunning, T. Shuzhuo, C. Liqin, and H. Jing, "Risk factors and countermeasures of adverse delivery trauma complicated with mental disorder in parturients," *China Maternal and Child Health*, vol. 27, no. 31, pp. 5022-5023, 2012.

[9] I. Lindberg, E. Mella, and J. Johansson, "Midwives' experiences of sphincter tears," *British Journal of Midwifery*, vol. 21, no. 1, pp. 7–14, 2013.

[10] R. E. Adams, C. R. Figley, and J. A. Boscarino, "The compassion fatigue scale: its use with social workers following urban disaster," *Research on Social Work Practice*, vol. 18, no. 3, pp. 238–250, 2008.

[11] J. W. Creswell, *Research Design: Qualitative, Quantitative And Mixed Methods Approaches*, SAGE Publications Inc, Thousand Oaks, 4th edition, 2013.

[12] B. H. Stamm, "The Concise ProQOL Manual [EB/OL]," [2016-01-01], https://www.proqol.org/uploads/ProQOL_Concise_2ndEd_12-2010.pdf.

[13] C. Figley and R. Charles, *Compassion Fatigue: Coping with Secondary Traumatic Stress Sisorder in Those Who Treat Thetraumatized*, BrunnerRoutledge, New York, NY, 1995.

[14] R. B. Johnson, A. J. Onwuegbuzie, and L. A. Turner, "Toward a definition of mixed methods research," *Journal of Mixed Methods Research*, vol. 1, no. 2, pp. 112–133, 2007.

[15] F. E. Tian, X. Chen, C. A. Mi et al., "Study on the present situation of nurses' compassion fatigue in psychiatric hospitals and its influencing factors," *Chinese Journal of Nursing*, vol. 52, no. 6, pp. 654–658, 2017.

[16] F.-E. Tian, X. Chen, C.-A. Mi, X.-J. Chen, Y. Jiang, and D.-H. Wang, "Current status and influencing factors of empathy fatigue among nurses in psychiatric hospitals," *Chinese Journal of Nursing*, vol. 52, no. 6, pp. 654–658, 2017.

[17] M. M. Tian, L. Fan, Y. Shi et al., "Analysis of the status quo of compassion fatigue of clinical nurses and its influencing factors," *Chinese Journal of Nursing*, vol. 53, no. 1, pp. 76–82, 2018.

[18] T. Meimei, F. Lin, S. Yan et al., "Current situation and influencing factors of clinical nurses' empathy fatigue," *Chinese Journal of Nursing*, vol. 53, no. 1, pp. 76–82, 2018.

[19] H. Rice and J. Warland, "Bearing witness: midwives experiences of witnessing traumatic birth," *Midwifery*, vol. 29, no. 9, pp. 1056–1063, 2013.

[20] C. Ming, Z. Xiaoping, L. Cong et al., "The status quo and countermeasures of obstetric nurses' job burnout under the two-child policy," *Journal of Nurses Training*, vol. 33, no. 8, pp. 724–726, 2018.

[21] C. Ming, Z. Xiaoping, L. Congxiang, M. Xuhong, Z. Jin, and W. Qian, "Current situation and countermeasures of job burnout of obstetric nurses under two-child policy," *Journal of Nursing Education*, vol. 33, no. 8, pp. 724–727, 2018.

[22] M WG, *A Study on the Status of Nursing Human Resources in Sichuan Province*, Sichuan University of China, Chendou, 2006.

[23] M. Weiguang, *Research on the current situation of nursing human resources in Sichuan Province*, Sichuan University, 2006.

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Retraction

Retracted: BERT-Based Clinical Name Entity Reorganization Model for Health Diagnosis

Disease Markers

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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) Peer-review manipulation

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.

References

[1] Y. D. Borole, A. V. Agrawal, M. Tesfayohanis, D. Thakkar, M. R. Abonazel, and F. A. Awwad, "BERT-Based Clinical Name Entity Reorganization Model for Health Diagnosis," *Disease Markers*, vol. 2022, Article ID 2297063, 12 pages, 2022.

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Research Article

BERT-Based Clinical Name Entity Reorganization Model for Health Diagnosis

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The National Health and Family Planning Commission requires medical institutions to use the International Classification of Diseases (ICD) codes. However, due to many commonly used words in clinical disease descriptions, the direct mapping matching rate between the diagnosis names entered in the electronic medical records and the ICD codes is low. In this paper, based on the actual diagnostic data on the regional health platform, a disease term map incorporating standard terms was constructed. Specifically, based on the rule algorithm based on the components of the disease, a data-enhanced BERT (bidirectional encoder representation from transformers) upper and lower relationship recognition algorithm is proposed. Synonymous upper and lower relationships identify diseases, and the hierarchical structure is further integrated. In addition, a task assignment based on the association map of disease departments is also proposed. Methods were used for manual verification, and finally, 94,478 disease entities formed a large-scale disease term map, including 1,460 synonymous relationships and 46,508 hyponymous relationships. Evaluation experiments show that, based on the disease term map and clinical diagnosis, the coverage rate of diagnostic data is 75.31% higher than direct mapping coding based on ICD. In addition, using the disease term map to code diseases automatically will shorten the coding time by about 59.75% compared with manual coding by doctors, and the correct rate is 85%.

1. Introduction

With the continuous improvement of informatization in the medical field, medical research institutions in Europe and the United States have established a series of medical terminology databases, such as the systematized nomenclature of medicine-clinical terms (SNOMED-CT) [1], the unified medical language system (UMLS) [2], ICD-10 (international classification of diseases 10th revision) [3], and ICD-11 (international classification of diseases 11th revision) [4]. Among them, the National Health Commission of the People's Republic of China clearly requires all medical institutions to uniformly use the Chinese version of ICD-10 (ICD10) in the writing of medical records, which greatly promotes the standardization and standardized management of medical services.

However, when ICD10 is actually applied to clinical data, less than 20% can directly establish the mapping. There are two main problems: first, the diversity of disease name descriptions. For example, “urinary tract infection” is a common term in clinical diagnosis, but it is not included in the ICD10. The word is a synonym for “urinary tract infection”; the corresponding code in ICD10 is N39.0. Second, the granularity of common disease terms is finer. For example, “diabetes with ocular changes” cannot find a matching synonym in ICD10, only its hyponym “diabetes” can be found, and the corresponding code of diabetes in ICD10 is E14.900. Therefore, using ICD10 as the standard to construct a disease term map that integrates common terms, and incorporating common terms as synonyms or hyponyms into ICD10, can effectively establish the mapping relationship between disease names and ICD10, which will facilitate doctors to find disease names or machine ICD automatic coding. However, the fusion of common terms requires a lot of medical knowledge, and the manual mapping is time-consuming and labor-intensive, and the accuracy of automatic machine mapping is relatively low. In addition, the classification system of ICD10 continues the traditional list structure, which is too flat and inconvenient to browse and search.

In view of the above problems and difficulties, this paper proposes a large-scale disease terminology map construction scheme that integrates common terms. Specifically, this paper screened out the common terms in the disease data of the Shanghai regional medical and health platform (which contains the clinical diagnosis and treatment information of 38 tertiary hospitals in the city) and integrated the common terms with ICD10. In addition, in order to facilitate doctors’ search, the category layer of ICD10 and the hierarchical structure of the Chinese version of ICD-11 (abbreviated as ICD11) were further integrated to form a large-scale disease term map fused with common terms. The construction of the disease term map combines the advantages of machines and humans. In the proposed scheme, firstly, the components of disease words are analyzed, and the synonymous relationship between diseases is identified by the rule algorithm based on disease components, and the upper and lower relationship between diseases is found through the data-enhanced BERT (bidirectional encoder representation from transformers) upper and lower relationship identification algorithm. Then, using the characteristics of the ICD system itself, according to the type of disease, the disease data is verified based on the subspecialty grouping. The main contribution of the paper includes the following aspects:

(1) Constructing a large-scale disease term map fused with common terms for clinical diagnosis data, the map can represent the hyponymous relationship and synonymous relationship between medical terms and fuse common terms with standard terms. In the end, 1460 synonymous relations and 46508 upper and lower relations were found

(2) Designing a task assignment method based on the association map of disease departments, which is convenient for proofreaders to verify medical data, so as to ensure the accuracy of the relationship between disease medical entities

(3) Experimental studies reveal that the disease term map constructed in this paper is efficient in terms of the coding coverage, coding efficiency, and coding accuracy when compared with the manual coding and ICD10 system

2. Related Work

There are abundant researches on the construction of terminology system at home and abroad. A large number of biomedical classification systems have been presented in the literature. In addition to the general classification systems such as UMLS [1] and SNOMED-CT, there are also subdivisions such as the drug-oriented naming system RxNorm [1], the inspection-oriented coding system LOINC [2], and the widely used International Classification of diseases system. The domestic medical terminology system is constantly in line with international standards, such as ICD10. The construction of the early terminology system is purely manual, such as the semantic-oriented English dictionary WordNet [2] and the common knowledge graph CYC [3], in which CYC consists of 500,000 entities and 7 million assertions.

In recent years, the use of automatic methods to construct terminology systems has been widely used. The construction process involves the problem of automatic classification and induction; that is, it can effectively expand the entire knowledge structure. A large number of works have studied methods based on language model matching to solve the problem of terminology and its relationship with the problem of automatic classification and induction of relations between hypernyms. For example, Demir et al. [4] described a method to automatically obtain hyponyms from unrestricted text, and determined a set of lexical-syntactic patterns that were easy to identify. Reference [5] proposed a graph-based approach aimed at automatically learning lexical taxonomies starting from domain corpora and the Web. Experiments show that high-quality results can be obtained both when constructing a completely new taxonomy and when reconstructing the WordNet subhierarchy. Reference [6] proposed a new algorithm to automatically learn the upper and lower (isGa) relations from text to solve the problem of automatically constructing and extending semantic taxonomies such as WordNet. Reference [7] proposed a new metric-based framework for the task of automatic classification and induction. In recent years, the use of word embedding-based methods to identify relations to reconstruct taxonomy is also very popular [8–11].

New information such as common terms is added to the existing taxonomy, mainly focusing on enhancing the WordNet taxonomy [12] enriched WordNet with 310,742 named entities and 381,043 “relationship instances.” Reference [13] created Medical-WordNet, which is not only a lexical expansion of medical terms in the original WordNet, but a new type of repository. Reference [14] studied the knowledge structure expansion problem, that is, how to add a large number of new concepts to the existing knowledge structure.

There are dual challenges to this problem, how to detect unknown entities or concepts and how to insert new concepts into existing knowledge structures without destroying the semantic integrity of newly created relationships. They propose a framework for ETFs to enrich large-scale general taxonomies with new concepts from sources such as news and research publications, linking new concepts to existing concepts and gaining potential parent-child relationships. However, the manual construction method requires a lot of manpower and material resources, and only the automatic construction method cannot guarantee the correct rate of the machine. Therefore, this paper adopts a method combining manual and automatic construction.

3. Construction of Disease Terminology Atlas

3.1. Problem Definition. This paper refers to and expands the classification hierarchy of ICD10 and ICD11 and defines the relationship between disease medical entities as follows:

Definition 1. Mapping relationship $R(E_i, E_j)$ between different disease medical entities. Among them, E_i and E_j are disease medical entities, and R is the mapping relationship. There are two types of mapping relationships:

(1) is_hypernym: relation is_hypernym (E_i, E_j) represents the upper and lower relationship between entities E_i and E_j. In particular, the is_hypernym relation is inversely functional: is_hypernym (E_i, E_j) $\Leftrightarrow$ is_hyponymy (E_i, E_j), that is, E_i is the hypernym of E_j, which is equivalent to E_j being the hyponym of E_i. For the sake of convenience, unless otherwise specified, the upper and lower relations in this paper refer exclusively to the upper and lower relations

(2) is_same: Relation is_same(E_i, E_j) represents the synonymous relationship between entities E_i and E_j. The synonymous relationship includes two parts: one is the medical synonymous relationship, similar to the synonymous relationship between "insulin-dependent diabetes mellitus" and "type 1 diabetes mellitus" The second is the synonymous relationship caused by the different writing habits of doctors, similar to the synonymous relationship between "type 1 diabetes" and "diabetes (type 1)".

The main task of this paper is to link common terms to ICD10 according to the relationship of disease medical entities and to fuse the category layer in ICD10 with the hierarchical structure of ICD11, so as to construct a large-scale disease term map that integrates common terms. Among them, common terms are defined as the names of diseases that appear more than 5 times in the clinically diagnosed disease data on the regional platform.

3.2. Overall Framework. The overall framework of this paper is shown in Figure 1. ICD10 fuses common terms, then adds ICD11 hierarchical structure information, and finally forms a disease term map fused with common terms. The left side of Figure 1 shows the basic framework of the disease term map. The fusion process is to determine whether the disease pairs with the standard disease terms in ICD10, and whether the common terms have a hyponymous relationship or a synonymous relationship. According to the disease medical entity relationship of the disease pair, the commonly used words are linked to each layer of the ICD10 to realize the classification of the commonly used words. The right side of Figure 1, respectively, shows the use of the disease component rule algorithm to identify whether the disease pair has a synonymous relationship, and the combination of BERT to identify whether the disease pair has an upper and lower relationship on the basis of the disease component based rule algorithm. Secondly, according to the mapping rules, the category layer in ICD10 is linked to the hierarchical structure of ICD11. Finally, in order to ensure the correctness of the fusion results, a task assignment method based on the association map of disease departments is introduced, which is convenient for verifiers to correct the relationship between disease medical entities contained in the disease term map.

3.3. ICD10 Fusion Phrases. For the task of identifying the relationship between disease terms, this paper defines it as the identification of synonyms and hyponyms, and the focus is on the identification of hyponyms. Reference [15] proposed a rule-based upper and lower identification algorithm, which is driven by knowledge and used for relationship judgment by preconstructing a dictionary containing a large number of fine-grained clinical entities and a set of upper and lower relations between entities. The rule-based method can identify the upper and lower relations with high quality, but limited by the size of the dictionary, its recall rate is very low. Therefore, on the basis of using the pretraining model combined with the reference results provided by the rules to provide auxiliary information, this paper proposes a data augmentation-based BERT upper and lower relationship recognition algorithm.

Given a disease pair (X_1, X_2), X_1 is the standard disease term in ICD10, and X_2 is the common term. Firstly, X_2 is sent to the rule algorithm based on disease components, and the optimal matching word X_3 of X_2 in the ICD10 corpus is obtained and the optimal matching pair (X_2, X_3). Next is the reference pair (X_3, X_1). Then, the disease pair (X_1, X_2) and the reference pair (X_3, X_1), respectively, go through BERT [16] to obtain the correlation representation [12] and [17] of the two elements in the word pair. Finally, concatenate [12] and [18], and use the feed forward neural network (FNN) to predict the upper and lower relationship.

In this paper, common terms and all the standard disease terms in ICD10 are formed into disease pairs, and the data-enhanced BERT epigenetic relationship recognition model is used to predict the hypostatic relationship of disease pairs, and all the prediction results are predicted as hyponymic relationships according to the model. The probability is sorted, and the highest probability (X_1, X_2) is taken as the final output result.

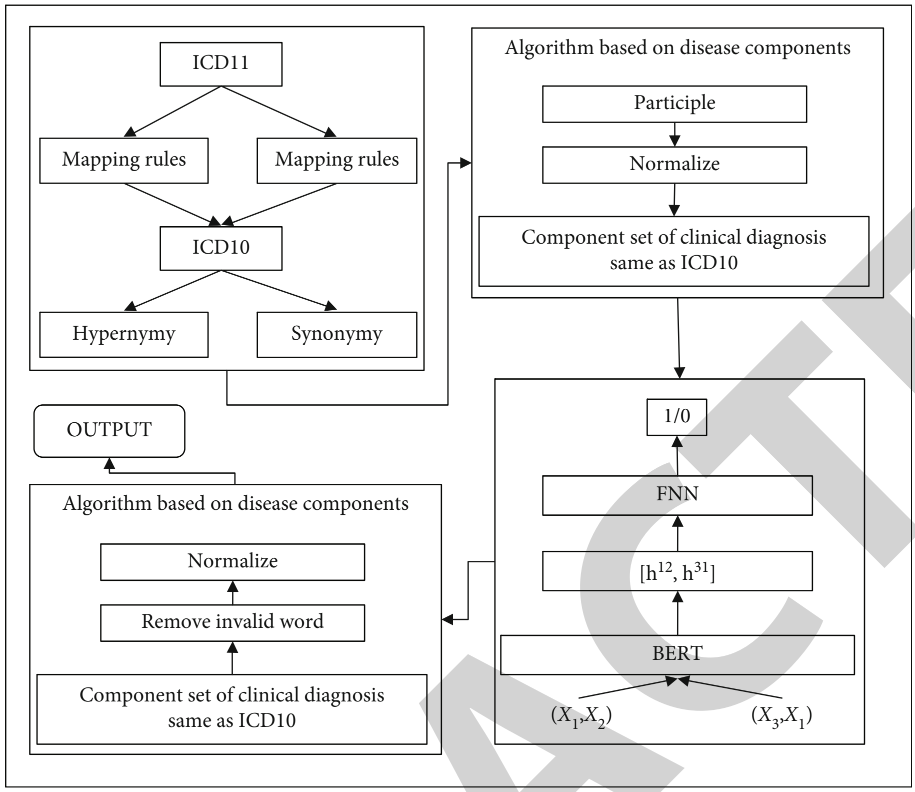

Figure 1: An overall framework for large-scale disease terminology map incorporating common terms.

3.3.1. Reference Pair Construction. The goal of constructing the reference pair (X_3, X_1) is to provide assistance for the identification of the upper and lower relationship between the disease pair (X_1, X_2), by judging the correlation between the reference results (X_3, X_1) predicted by the rule algorithm based on disease components information. Therefore, this paper defines the disease components to obtain the corresponding dictionary and uses the rule algorithm based on the disease components to obtain X_3.

(1) Definition of disease components: based on the analysis of the clinical diagnosis data of 38 hospitals included in the ICD and regional medical platform, this paper summarizes the disease words into atomic disease words, causal words, pathological words, and parts. Part words and clinical expression words are composed of five major components. Table 1 gives the specific meanings

(2) The rule algorithm based on disease components gives the disease name set $D = \{D_1, D_2, D_n\}$ of ICD10, where n is the total number of disease names. The rule algorithm based on disease components firstly segmented D_i and X_2 based on the bidirectional maximum matching algorithm of disease components and eliminated the invalid words "accompanied by" etc. Then, replace the remaining words with their corresponding standard names, thereby obtaining valid element sets set$D$ and set$X$, respectively. For the elements in the valid element sets set$D$ and set$X$ of D_iX_2, this paper iteratively replaces the hyponymous disease components with their hypernyms to detect the epistasis relationship, until the following situations occur

If set$X$ contains set$D$, then D_i is the hypernym of X_2 and returns the number of subsituations; otherwise, continue to perform hypernym substitution until there is no hypernym to replace. Finally, set X_3 as D_j satisfies the hypernym condition and has the least number of substitutions. The pseudocode of the algorithm is shown in Algorithm 1.

The problem of identifying the semantic relationship of disease medical entities based on the BERT hypernym relationship recognition algorithm based on data enhancement can be regarded as a classification task, that is, whether the standard disease term X_1 in the ICD10 is a hypernym of the common term X_2. The model architecture is shown in Figure 2.

This paper uses the pretrained language model BERT to encode disease pairs X_1, X_2 and reference pairs X_3, X_1, respectively. Taking the disease pair X_1 and X_2 as an example, the [SEP] tag is used to identify the segmentation information of the two disease words, and a special tag [CLS] is added at the beginning of the input sequence to form "$[CLS] X_1\ [SEP]\ X_2\ [SEP]$" as input. The model first calculates the input embedding, which includes the sum of word embedding, sentence embedding, and position embedding. Then, the input embedding is sent to the bidirectional

Table 1: Examples of disease components.

Disease components meaning	Disease components meaning
Atomic disease words	Atomic disease words: a part of a disease name, but not divide into finer grained words, such as diabetes
Causal words	Including the cause of disease and conditions. The cause of disease refers to those factors that can cause the disease and give the disease specificity, for example, hereditary
Pathological words	Modifying words such as severity, nature, and period of onset. For example, pregnancy is the pathological word of "gestational hypertension"
Part words	Indicating the location of disease in disease name. For example, stomach is the part word of "gastric ulcer"
Clinical expression words	A series of abnormal changes in a patient's body after he has a certain disease, such as "fever"

Input: Standard disease terms X_1in ICD10, common terms X_2in clinically diagnosed disease data, synonymous relation set R in the dictionary of disease components, stop word set $S = \{S_1, S_2, ..S_n\}$, disease components HypernymMap in the lexicon;
Output: The relationship of disease to (X_1, X_2)Perform word segmentation on (X_1, X_2) according to the bidirectional maximum matching algorithm, and obtain the components of $X_1 = \{X_{11}, X_{12}, \cdots .X_{1m}, X_2 = \{X_{21}, X_{22}, \cdots .X_{2n}\}$
for $X_{2i} \in X_2$ *do*
if $X_{2i} = S_i$ *then*
Move X_{2i} out of X_2
elseif X_{2i} in R *then*
Replace X_{2i} *with* the *standard synonym* in R ;
endif
endfor
Do the *same steps* 2 to 8 for X_1 ;
Obtain the *effective component set setX* of X_2 and the \ *effective component set setD* of 1 *respectively* ;
if setX − *setD* = ∅*then*
return synonymous relation ;
else if *setD* ∈ *setX then*
return upper − *lower relationship* ;
else while X_{2i} in *setX has hypernym* in *HypernymMap do*
Replace X_{2i} *with its hypernym counterpart* X_{2i} ;
if setX − *setD* = ∅*then*
return synonymous relation ;
break ;
else if setD ∈ *setX then*
return upper and *lower relationship* ;
break ;
endif
end while
return irrelevant
end if

Algorithm 1: Rules of algorithm based on disease components.

transformer model, and the output [CLS] contains the information about whether the two disease words are related. The final output [18] of the labeled [CLS] is used as the correlation representation in the classification task vector. Similarly, the reference pair X_3, X_1 is sent to BERT to get [19]. Finally, [20], [21] are concatenated and sent to the feed forward neural network, and the output result is 0/1 (0 means there is no relationship between the two, and 1 means that X_1 is the upper and lower relationship of X_2).

3.3.2. Comparison Experiment of Term Graph Relationship Recognition Algorithm. This paper verifies the effectiveness of the algorithm used in constructing a disease term graph that integrates common terms. We use the disease data in the regional medical platform as the experimental data set. In particular, there are few synonymous relationships between disease names in this dataset, so the rule algorithm based on disease components is directly used to judge the synonymous relationship, so this paper only conducts comparative experiments on the upper and lower relationship.

This paper selects four relationship recognition algorithms for comparison:

(1) String similarity algorithm: first, find out the Levenshtein distance (X_1, X_2) between the standard disease term X_1 and the common term X2 in

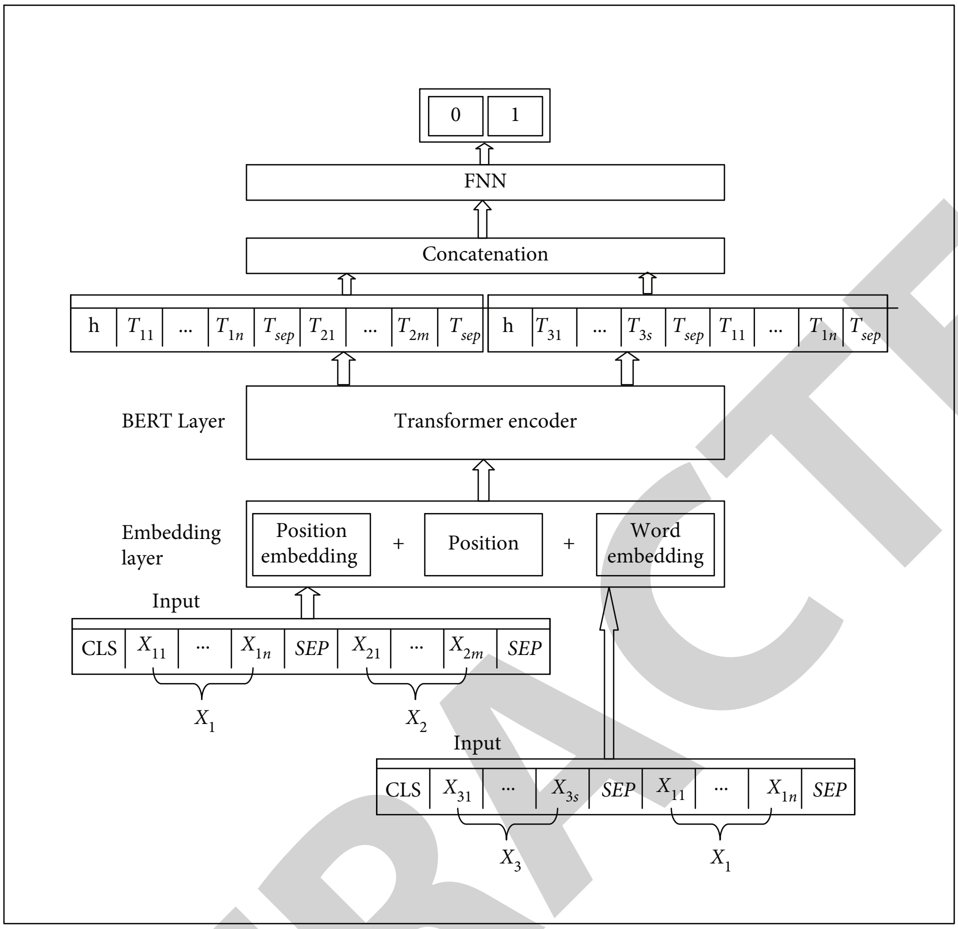

Figure 2: Algorithm model of BERT upper and lower relationship recognition based on data enhancement.

ICD10 for each disease pair. The Levenshtein distance refers to the minimum editing operation required to convert two strings from one to the other frequency. If the result of distance (X_1, X_2) exceeds the threshold, it is considered that X_1, X_2 have an upper-lower relationship; otherwise, there is no relationship. The threshold set in this paper is 0.8

(2) Dynamic distance loss model: Reference [11] trains a hyponym vector O_{X_2} and a hypernym vector E_{X_2} for each common phrase X_2. Whenever X_2 appears as a hyponym, use O_{X_2}; whenever it appears as a hypernym candidate, use E_{X_2}. Then, use the supervised corpus to train the SVM model, and use the trained model to judge whether the input disease pair (X_1, X_2) is a hypernym pair

(3) Rule algorithm based on disease components: according to Reference [15], the disease pairs (X_1, X_2) are firstly segmented according to the dictionary, and the elements after word segmentation are subjected to stop words and standardization operations. If the elements of X_1 are included in the elements of X_2, then X_1 is the hypernym of X_2, otherwise, iteratively replaces that element of X_2 with its hypernym

(4) BERT reference [16]: input the disease pairs (X_1, X_2) in the form of $''[CLS]\, X_1\, [SEP]\, X_2\, [SEP]''$ into the pretraining model BERT, followed by a feed-forward neural network for binary classification

For the relationship identification results, the evaluation indicators in this paper use the most commonly used Precision, Recall, and $F1\_score$ as the evaluation criteria. The calculation formula of the evaluation results is

$$\text{Precision} = \frac{\text{Number of right relationships}}{\text{Total number of relationships}} \times 100\%,$$
$$\text{Recall} = \frac{\text{Number of right relationships}}{\text{Total number of relationships in standard results}} \times 100\%,$$
$$F1_{\text{score}} = \frac{2 \times \text{Precision} \times \text{Recall}}{\text{Precision} + \text{Recall}} \times 100\%. \quad (1)$$

Table 2 and Figure 3 show the Precision, Recall, and F 1_score of the five comparison algorithms. Compared with the existing algorithms, the proposed algorithm obtains the

Table 2: Comparative experimental results.

Algorithm	Precision	Recall	F1_score
String similarity algorithm	96.56	80.03	72.97
Dynamic distance loss model	72.32	88.73	80.36
Rule algorithm based on disease components	95.52	22.12	36.23
BERT	94.63	91.84	93.52
Proposed method	96.89	92.28	94.70

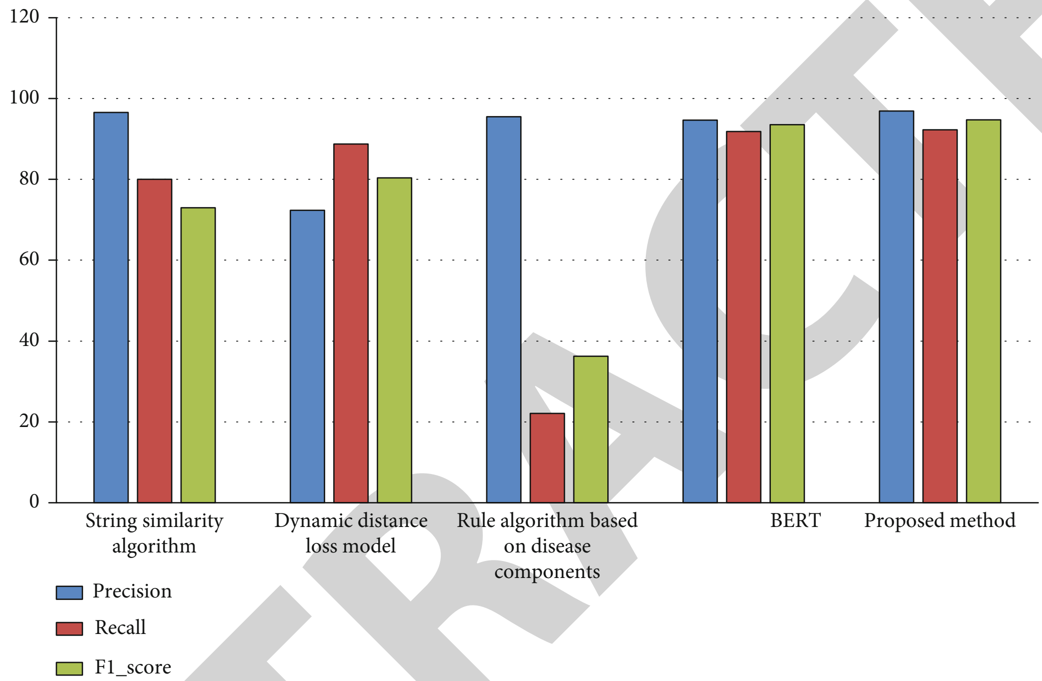

Figure 3: Comparative experimental results.

best F1_score value, and Precision, Recall, and $F1$_score are 96.89%, 92.28%, and 94.70%, respectively. For the rule-based relationship recognition method, its Precision reaches 100%, but the Recall is very low, because the algorithm is limited by the size of the dictionary and does not cover completely, but its prediction results have high confidence. This is also the reason why this paper integrates the algorithm to provide auxiliary information. In addition, we found that the $F1$_score value of the proposed algorithm is 0.92% higher than that of using BERT alone, which proves the effectiveness of the data augmentation-based BERT subordinate relationship recognition algorithm.

3.4. Add ICD11 Hierarchy Information. With the help of the mapping table published on the official website of ICD10 and ICD11, this paper links all category-level diseases in the ICD10 structure that incorporates common terms to the ICD11 hierarchy to add ICD11 hierarchy information to obtain a more fine-grained disease hierarchy. The structure is convenient for doctors to view and screen diseases. The reason for adding ICD11 hierarchy information is as follows:

(1) The hierarchical structure of the 3-digit category code of ICD10 is too flat and fails to reflect the hierarchical structure of diseases. "diabetes" and "endocrine diseases" are on the same level in ICD10, and "diabetes" should belong to "endocrine diseases"; that is, "diabetes" should be located at the lower level of "endocrine diseases"

(2) The classification of diseases is becoming more and more refined. ICD11 adjusts the classification axis, changes the classification level, adds or refines taxonomic units, and revises and improves the original classification structure and classification knowledge of ICD10. However, in view of the fact that medical institutions have used ICD10 as a disease code in the past 10 years, therefore, it is necessary to use ICD10 to fuse with common terms first and then add the hierarchical structure information of ICD11

The classification code of the ICD10 standard is firstly the category, which is divided into suborders with a total of three levels. In this paper, ICD10 category layer diseases are mapped to ICD11 diseases at any layer, and it is found that ICD10 category layer can map 90.34% of the diseases in ICD11, so the diseases in the category layer in ICD10 (2047 in total) are mapped to the ICD10 category layer diseases. The results of each layer node of ICD11 are shown in Table 3 and Figure 4. A total of 2521 items are mapped in Table 3, while there are 2047 items in the ICD10 category level diseases, and the reason for the extra 474 items is that 213 items are not uniquely mapped. For example, "Other bacterial enteric infections" (code A04) in the ICD10 category layer is further split into "Other Vibrio enteric infections" (code 1A01) and "Escherichia coli" in ICD11. "Intestinal infection" (code 1A03), "bacterial intestinal infection, unspecified" (code 1A02) result in nonunique mappings. Therefore, it is necessary to further align the ICD10 suborder and detail layers with the ICD11 multiple mapping, and this requires the intervention of professional medical staff, so this paper uses the task assignment method based on the association map of disease departments to perform knowledge verification on the large-scale disease term map constructed with the fusion of common terms.

3.5. Knowledge Verification. Even after data enhancement, the upper and lower relationship recognition algorithms based on the above still cannot guarantee that the predicted upper and lower relationships are all correct, and two types of errors may occur:

(1) Common terms are related to wrong ICD10 names. For example, "type 2 diabetic neuropathy" has an upper and lower relationship with "type 2 diabetic neuritis" through an algorithm, and the correct one should be "type 2 diabetes with neurological complications"

(2) The name of ICD10 is not a direct hypernym of common expressions. In this paper, the most adjacent hypernyms in the hierarchy of common terms are called direct hypernyms. The hypernym relationship is transitive; that is, X is the direct hypernym of Y, Y is the direct hypernym of Z, and X is the hypernym (nondirect hypernym) of Z. For example, "type 2 diabetic macro albuminuria" has an upper and lower relationship with "type 2 diabetes" through an algorithm, and "type 2 diabetic nephropathy" is the direct hypernym of "type 2 diabetic macroa lbuminuria". The judgment and correction of the above situations depend on deeper domain knowledge, and in order to ensure the medical correctness of the disease terminology map, manual work is needed

The departments corresponding to the standard disease terms in the disease pair are divided into multiple department-based term subsets to be verified. The same subset of terms to be verified will be assigned to multiple proofreaders in the same department for verification and modification. After completion, it will be automatically judged by the machine, and the data with the reliability of the verification result higher than 0.5 will be classified. For the correct term set, the rest will be checked by experts.

Table 3: ICD10 category layer mapped to the mapping of each layer of ICD11.

ICD11 hierarchy	Mapping number	Mapping percentage (%)
3rd	688	28.11
4th	1049	45.75
5th	582	22.80
6th	115	5.06
7th	17	0.50

(1) Assignment of tasks based on the department where the disease is located. For the standard disease terms and common terms in the disease pair ICD10, firstly, according to the added hierarchical structure information of ICD11, the standard disease terms in the disease pair are roughly classified according to chapters, and then use the disease department knowledge map we constructed previously. The standard disease terms under each chapter are subdivided by departments, and the disease pairs that are finally classified into the same department will be filled in the same knowledge verification form, and the hierarchical structure of their standard disease terms will be expanded

(2) Manual proofreading: the same task will be assigned to n ($n \geq 3$) medical staff for verification, in order to reduce the randomness and chance of verification results. In response to the wrong ICD10 name on the link of common words, the medical staff modified the knowledge verification table (the hierarchy of the term base where the common term is located), it is judged whether the common term is a direct hypernym, and the corresponding modification is made. In the manual proofreading process, if all proofreaders have not modified a certain piece of data, the piece of data will be directly added to the correct term set

(3) Proofreading consistency judgment: when multiple people proofread the same piece of data, there will be a variety of modification situations. In view of the inconsistency of multiperson proofreading results, it is necessary to evaluate the quality of proofreading results. For the results of manual proofreading, the specific quality assessment is as follows: each piece of data to be proofread is regarded as a proofreading task T_i, and each proofreading task T_i is guaranteed to have n ($n \geq 3$) proofreaders to check. Each proofreader may have m kinds of proofreading results in a verification task d_i. Therefore, the confidence level of each proofreading result is calculated as

$$td_j = \frac{n_j}{n} (j = 1, 2, \cdots \cdots, m) \quad (2)$$

Among them, n_j represents the number of people who

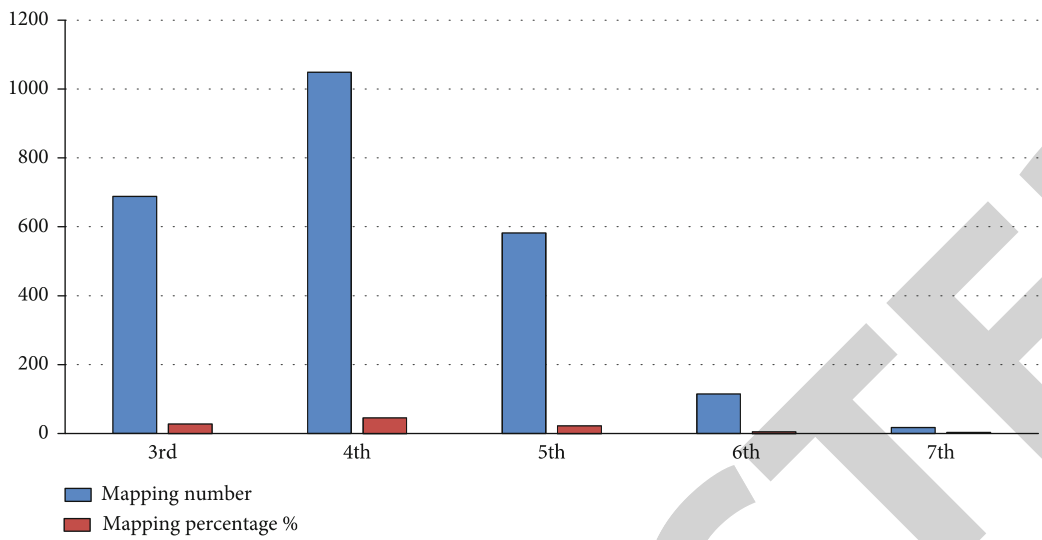

FIGURE 4: ICD10 category layer mapped to the mapping of each layer of ICD11.

TABLE 4: Disease name code mapping (%).

Coding mode	Mapping rate of data coding	
	The 1st group	The 2nd group
Coding based on ICD10	11.96	12.01
Coding based on our method	95.69	74.37

choose the jth proofreading result. If $td_j > 0.5$, the result of the jth proofreading task of this proofreading task T_i is correct, and the correct term set will be output directly; otherwise, T_i will be checked by medical experts.

(4) The man-machine combination method saves labor costs. First, for each common term, the algorithm predicts its position in the ICD10. Although this may not be exact, the assignment of the subtree of terms in which it resides is generally accurate. For example, "type 2 diabetic neuropathy" and "type 2 diabetic macro albuminuria", are both subtrees of the term "type 2 diabetes mellitus". This ensures that the data search space is reduced from ICD ensemble search to subtree search. Moreover, diabetes belongs to the department of endocrinology as a whole, and the assignment of specialist proofreading personnel is also correct, which ensures that personnel can check familiar diseases

4. Disease Term Coding Assessment

4.1. Assess Coding Coverage. In order to verify that the disease term map constructed in this paper can effectively cover more clinical diagnostic data, we extracted 10,038 data from the electronic medical record (EMR) discharge summary table as the first group of evaluation data and from the follow-up data. 9426 pieces of data were extracted as the second group of evaluation data, and the number of successful mapping of disease coding based on ICD10 and the disease term map constructed in this paper was counted. The mapping results are shown in Table 4 and Figure 5.

It can be seen from Table 4 that using the disease term map constructed in this paper can increase the coding coverage rate by 74.37% on average compared to the one based on ICD10, which proves that more disease-corresponding codes can be found using the disease term map. However, the disease term map constructed in this paper still fails to find all the medical entity relationships of diseases, and the reasons include two aspects: (1) due to the fact that there are two disease names in the real data. For example, the disease name "neonatal convulsion (epilepsy)", in which "neonatal convulsion" corresponds to P90 in ICD10, the corresponding code of "epilepsy" in ICD10 is G40.901, and "neonatal convulsion" and "epilepsy" are two diseases, and it is difficult for the disease term map to distinguish the disease code according to the algorithm. (2) Data that is not the name of the disease appears in the real data, such as "after autologous stem cell transplantation" and "after posterior urethral valve operation". For the first case, different weights can be set for disease names containing two codes according to the symbols. For the second case, the occurrence of data with nondisease names should not have been linked to the Disease Terminology Atlas.

4.2. Evaluate Coding Efficiency. In order to verify the advantages of the large-scale disease term map constructed in this paper fused with common terms in the medical field when doctors fill in disease codes, we set up two evaluation methods, manual coding and machine-assisted coding, in order to compare the constructed disease term map for doctors. For the effect of coding disease efficiency for manual coding, we recruited 5 medical staff who were familiar with ICD codes, given the ICD10 disease standard classification codes, and counted the completion time of 5 testers to find out the matching codes for 50 randomly sampled disease names.

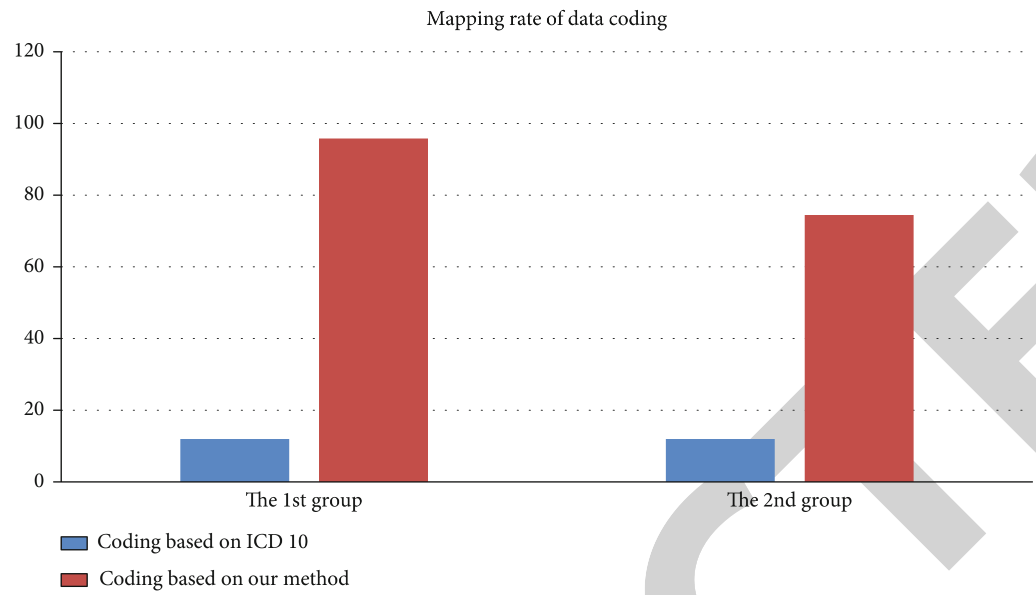

Figure 5: Disease name code mapping (%).

Table 5: Completion time results for human coding and machine-assisted coding.

Proofreader	Manual coding (s)	Machine-aided coding (s)
1	475.017	196.423
2	392.206	162.221
3	412.157	160.871
4	466.403	171.990
5	468.183	179.015
Average	440.102	169.939

For machine-assisted coding, we first used the disease term map constructed in this paper to automatically find the ICD10 codes corresponding to 50 disease names and displayed them in the form of the knowledge verification table. The completion time at this time is defined as the sum of the machine running time and the time spent by the proofreader. The experimental results are shown in Table 5 and Figure 6. The completion speed of the auxiliary coding using the disease term map constructed in this paper is 2.48 times that of manual coding, indicating that using the disease term map constructed in this paper to automatically perform disease coding can shorten the coding time for doctors. In practice, the medical staff of medical institutions are not too familiar with the ICD coding system, which will also affect the coding efficiency, and with the increase in the amount of disease data, the application of the disease term map constructed to the filling process of the first page of medical records have more prominent advantages.

4.3. Evaluate Coding Accuracy. The validity of the disease term map constructed in this paper is verified by using the electronic health record (EHR) data of the regional platform. The data includes the registration data of 38 tertiary hospitals in Shanghai, and the data containing the doctor code accounts for 536,456 pieces, and the data is cleaned. After that, 2 special disease data were randomly selected as evaluation data. The goal of this evaluation is to count the respective accuracy of the doctor's manual coding and the coding using the disease term map constructed in this paper. The results are shown in Table 6. It is worth noting that the standard ICD code of the evaluation data is based on the ICD10 code obtained after knowledge verification.

From the results in Table 6, it can be seen that the correct rate of disease term map coding constructed in this paper is much higher than that of doctors' manual coding, which is increased by 60%. Analyze the reasons for the low accuracy rate of doctors' manual coding: (1) doctors have inconsistent understanding of coding. For the disease name "type 2 diabetic ketosis", the doctor's coding includes E11.103, E11.100, and FFF. The code of the disease term map is E11.100. After verification by the proofreaders, it is synonymous with "type 2 diabetic keto acidosis", and the code should be E11.100.2 some doctors fill in the disease code irregular. For example, the commonly used term "stage IV gastric malignant tumor" should be linked to "stomach malignant tumor" (coded as C16.900) in ICD10, and the doctor code is C16. Another example is the commonly used term "type 2 diabetes", which corresponds to "type 2 diabetes" in ICD10 (coded as E11.900), while the doctor's code is written as E11.90000S.

The above-mentioned experimental study shows that the disease terminology map constructed in this paper not only maintains the existing standard system but also takes into account the convenience of clinical use. The disease term map was evaluated from three aspects: coding coverage, coding efficiency, and coding accuracy. Compared with the ICD10 system, the disease term map constructed can cover 75% more on average. Compared with manual coding, the use of disease term atlas-assisted coding can shorten the time by about 59.75%, and the accuracy rate reaches 85%.

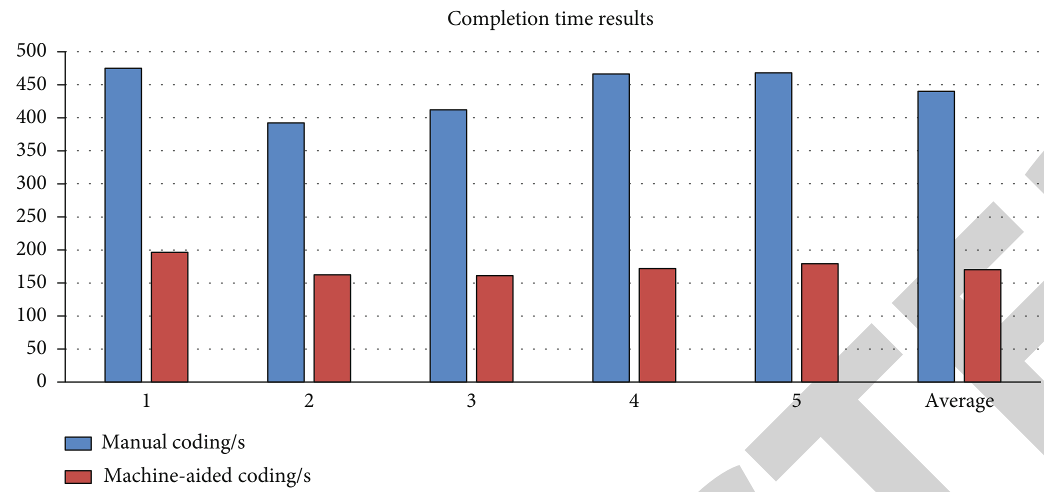

FIGURE 6: Completion time results for human coding and machine-assisted coding.

TABLE 6: Manually coded by physicians and automatically coded using the Disease Terminology Atlas.

Coding mode	Accuracy (%)
Doctor manual coding	68.56
Coding based on our method	83.48

5. Conclusion

In this paper, the disease medical entity relationship between common terms and standard disease terms in ICD10 is identified through the rule algorithm based on disease components and the BERT hypernymous relationship recognition algorithm based on data enhancement, and the mapping between common terms and ICD10 codes is realized, and the ICD11 code is added. The hierarchical structure is convenient for doctors to check the ICD10 code corresponding to the disease. Disease coding using the disease term map constructed in this paper has good performance in coding coverage, accuracy, and coding efficiency. In the future, the disease term map can be applied in various medical structures to ensure the coverage, efficiency, and accuracy of disease coding and to promote the standardization process of medical information.

Data Availability

All the data are available on miretab@dadu.edu.et.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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References

[1] E. Ennadifi, S. Laraba, D. Vincke, B. Mercatoris, and B. Gosselin, "Wheat diseases classification and localization using convolutional neural networks and GradCAM visualization," in *2020 International Conference on Intelligent Systems and Computer Vision (ISCV)*, pp. 1–5, Fez, Morocco, 2020, June.

[2] B. Lei, P. Yang, T. Wang, S. Chen, and D. Ni, "Relational-regularized discriminative sparse learning for Alzheimer's disease diagnosis," *IEEE Transactions on Cybernetics*, vol. 47, no. 4, pp. 1102–1113, 2017.

[3] D. Mahapatra, A. Poellinger, L. Shao, and M. Reyes, "Interpretability-driven sample selection using self supervised learning for disease classification and segmentation," *IEEE Transactions on Medical Imaging*, vol. 40, no. 10, pp. 2548–2562, 2021.

[4] J. Cai, A. Liu, T. Mi et al., "Dynamic graph theoretical analysis of functional connectivity in Parkinson's disease: the importance of fiedler value," *IEEE Journal of Biomedical and Health Informatics*, vol. 23, no. 4, pp. 1720–1729, 2019.

[5] Z. Lin, S. Mu, F. Huang et al., "A unified matrix-based convolutional neural network for fine-grained image classification of wheat leaf diseases," *IEEE Access*, vol. 7, pp. 11570–11590, 2019.

[6] J. Hariharan, Y. Ampatzidis, and J. Abdulridha, "The basis for development of a foundational biomarker reflectance signature database system for plant cell identification, disease detection, and classification purposes," in *2020 10th Annual Computing and Communication Workshop and Conference (CCWC)*, pp. 0881–0887, Las Vegas, NV, USA, 2020, January.

[7] Y. Yin, X. Yang, J. Xiong, S. I. Lee, P. Chen, and Q. Niu, "Ubiquitous smartphone-based respiration sensing with Wi-Fi signal," *IEEE Internet of Things Journal*, vol. 9, no. 2, pp. 1479–1490, 2022.

[8] M. M. D. Quintana, R. R. D. Infante, J. C. S. Torrano, and M. C. Pacis, "A hybrid solar powered chicken disease monitoring system using decision tree models with visual and acoustic imagery," in *2022 14th International Conference on Computer and Automation Engineering (ICCAE)*, pp. 65–69, Brisbane, Australia, 2022, March.

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Research Article

Prediction of Protein-Protein Interaction Sites by Multifeature Fusion and RF with mRMR and IFS

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Prediction of protein-protein interaction (PPI) sites is one of the most perplexing problems in drug discovery and computational biology. Although significant progress has been made by combining different machine learning techniques with a variety of distinct characteristics, the problem still remains unresolved. In this study, a technique for PPI sites is presented using a random forest (RF) algorithm followed by the minimum redundancy maximal relevance (mRMR) approach, and the method of incremental feature selection (IFS). Physicochemical properties of proteins and the features of the residual disorder, sequence conservation, secondary structure, and solvent accessibility are incorporated. Five 3D structural characteristics are also used to predict PPI sites. Analysis of features shows that 3D structural features such as relative solvent-accessible surface area (RASA) and surface curvature (SC) help in the prediction of PPI sites. Results show that the performance of the proposed predictor is superior to several other state-of-the-art predictors, whose average prediction accuracy is 81.44%, sensitivity is 82.17%, and specificity is 80.71%, respectively. The proposed predictor is expected to become a helpful tool for finding PPI sites, and the feature analysis presented in this study will give useful insights into protein interaction mechanisms.

1. Introduction

Proteins interact with other proteins, DNA, RNA, and chemicals to play key roles in practically all biological events. Without initially defining the characteristics of contact sites, it is impossible to define the protein molecular structures. Proteins seldom act independently; instead, they are frequently part of a larger molecular network, with parts coordinated by complex protein-protein interaction (PPI) regulatory networks [1]. PPIs are important for practically every aspect of cellular function, including metabolic control, gene translation, DNA structure, and protein synthesis. Discovering the binding sites among interacting proteins, in particular, provides crucial information on the function of a protein and the elemental composition of associated proteins, assisting in the identification of biological targets and leading drug design. As a result, molecular recognition relies eavily on solving the issue of identifying interaction points [2].

Previously, a large number of properties that have some predictive potential for interfaces have already been identified [3, 4]. They are composed of three methods: the first uses sequence information alone to predict protein interfaces, the second applies structural information to improve sequences that are then used to build predictors, and the third method predicts using only 3D structure and sequence information [5].

Several approaches for predicting PPI sites have already been presented. Based on the utilized protein characteristics, they can be divided into three types. The first class's methods are solely dependent on sequence information. Ofran and Rost [6] employed a dataset, which consisted of 1,134 chains in 333 complexes and 59,559 touching residues. In their study, they correctly identified the PPI site in 20% of the complexes with 70% of their predictions being correct. The second class of methods combines secondary structure and sequence information. Zhou and Shan [7] established a predictor that was trained on 615 nonhomologous complex-forming protein pairs and tested on 129 nonhomologous complex-forming protein pairs. In their study, 70% of interface residues were properly predicted. Wang et al. [8] obtained an accuracy of 65.4% and a correlation value of 0.297 using a nonredundant data set of 69 protein chains. The third class uses 3D information of structures sequence information to make predictions. Aytuna et al. [9] proposed a technique that was evaluated sequentially nonredundantly on 67 interfaces and a nonredundant dataset of 6,170 protein structures. Public databases such as the Biomolecular Interaction Network Database, the database of Interacting Proteins, and PDB validated the majority of the 62,616 probable relationships. Sikic and Tomic [10] suggested a sequence-based prediction approach that has an 84% accuracy rate and a 26% recall rate. When structural information is included, prediction performance improves to 76% precision and 38% recall.

Several machine learning techniques have been developed to identify PPI sites based on various types of information. The author in [11] evaluated using a support vector machine (SVM) 50 randomly selected proteins and reported 60.6%, 53.4%, and 0.243 sensitivity, specificity, and MCC, respectively. Bradford et al. [12] used a Bayesian network to predict PPI sites with an 82% accuracy on a dataset of 180 proteins. Although great achievements have been made, the results still face difficulties to address the problem of predicting interaction sites [13]. Challenges remained to be overcome. First, the key biological features for properly defining protein-protein interaction sites have yet to be thoroughly identified. There is no way to identify interaction interfaces from other surface patches using a single parameter. As a result, several studies were conducted for the prediction of PPI sites using a combination of features. [14]. Second, present approaches for predicting PPI residues frequently rely on information taken directly from amino acid sequences, which is insufficient to extract all relevant information. Finally, in the prediction of protein interaction sites, a skewed class distribution problem is common [15]. A protein's number of interaction sites is generally substantially lower than its number of noninteracting sites. Overfitting and poor performance are common outcomes of such an imbalance, which is especially true for data in the interacting class [16].

In this study, a new approach is presented for identifying PPI sites, combining RF and mRMR, followed by IFS. To predict PPI sites, we used physiochemical properties, sequence conservation, residual disorder, secondary structure, and eleven 3D structural features. The datasets used in this study are derived by following methods. Firstly, the individual proteins are extracted from a set of 70 protein-protein heterocomplexes. Proteins with sequence identity less than 30% are subsequently obtained after removing redundant proteins and molecules with less than 10 residues. Some proteins that are not available in HSSP and DSSP programs are also omitted. As a result, 99 polypeptide chains are extracted from 54 heterocomplexes, which can be grouped into six categories. The categories and the number of representatives in each category (the values in the parentheses) are as follows: antibody antigen (29), protease inhibitor (19), enzyme complexes (14), large protease complexes (8), G proteins (13), and miscellaneous (16). The DSSP program works by calculating the most likely secondary structure assignment given the 3D structure of a protein. It does this by reading the position of the atoms in a protein followed by calculation of the H-bond energy between all atoms. The algorithm will discard any hydrogens present in the input structure and calculates the optimal hydrogen positions by placing them at 1.000 Å from the backbone N in the opposite direction from the backbone C=O bond. The best two H-bonds for each atom are then used to determine the most likely class of secondary structure for each residue in the protein. The surface residues are defined based on their relative solvent accessible surface area (RASA), which is calculated by the DSSP program. A residue is considered as a surface residue if its RASA is greater than 25%. A total of 13,771 surface residues are collected from all these polypeptide chains. Furthermore, a surface residue is defined to be an interface residue if its calculated ASA in the complex (CASA) is less than that in the monomer (MASA) by at least 1 Å^2. This way, the number of protein-protein interaction sites is about 10% (2,828 residues) of the whole set of residues contained in the selected polypeptide chains (27,442 residues). Therefore, a total of 2,828 interaction sites are obtained as positive samples and 24614 noninterface residues are defined as negative samples. We predicted the PPI sites by both sliding window and patch analysis methods using the datasets; the results showed that the accuracy of the sliding window is superior to patch analysis. The proposed predictor outperformed numerous other state-of-the-art predictors in terms of accuracy, sensitivity, and specificity, with an average prediction accuracy of 81.44%, a sensitivity of 82.17%, and specificity of 80.71%.

The rest of the manuscript is ordered as: Section 2 provides a detailed description of the proposed method and data collection. Different feature selection methods and classification algorithms are discussed in this section. Section 3 illustrates the results, and the conclusion is presented in Section 4. All authors contributed equally in this research.

2. Methodology

The proposed methodology is given in Figure 1.

2.1. Dataset. In this study, the PPI datasets were retrieved from the dataset developed by Jones and Thornton [17]. A total of 99 polypeptide chains were recovered from the 54 heterocomplexes in the sample. All proteins were taken from the Protein Data Bank (PDB) at http://www.pdb.org.

First, we determined the RASA of all surface residues detected by the DSSP algorithm [18]. If a residue's RASA is greater than 25%, it is classified as surface residue. Amino acid solvent exposure is essential for investigating and forecasting protein interaction and function. Half-sphere exposure (HSE), contact number (CN), residue depth (RD),

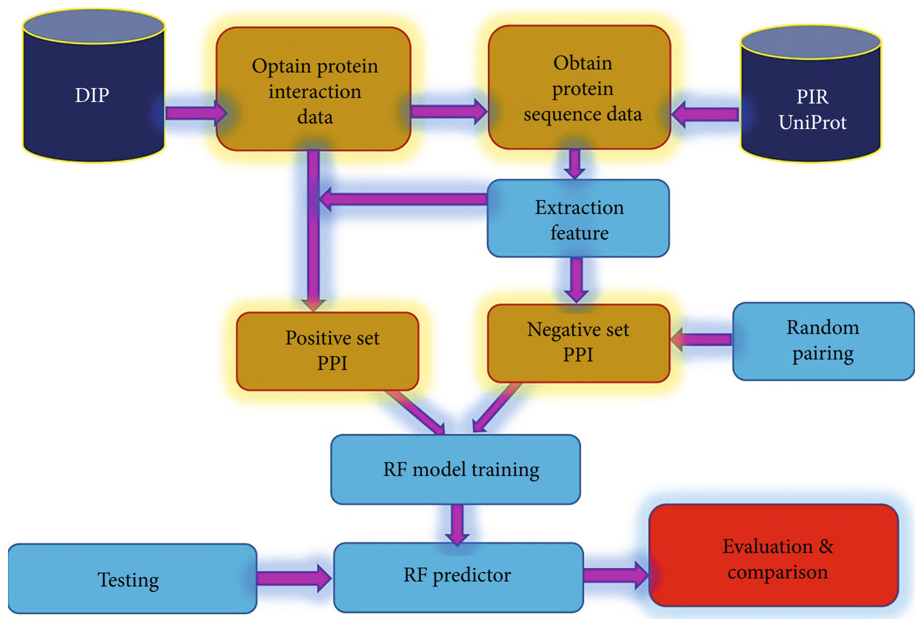

Figure 1: Propose methodology.

Table 1: For a single residue of feature space prediction results.

Dataset	Sensitivity	Specificity	Precision	Accuracy	MCC
Single	0.267	0.980	0.787	0.835	0.390

accessible surface area (ASA), and relative accessible surface area are only a few of the different elements that make up solvent exposure features (RASA). Predicting protein-protein interaction hotspots has been done widely and successfully using the available solvent [19]. Solvent accessibility has the drawback of being unable to reveal any information regarding completely submerged leftovers. Half-sphere exposure (HSE), in contrast to conventional solvent access, can more accurately depict the local surroundings of the target residue from a different angle. The average atom depth of target residue atoms is represented by RD, and the number of residues within a given radius is represented by CN [20]. There were 13,771 surface residues. If the RASA in the complex (CASA) is less than the RASA in the monomer (MASA) by at least one unit, the surface residue is classified as an interface residue [21]. This way, the number of PPI sites in the selected polypeptide chains is about 10% (2,811 residues) of the total number of residues (27,442 residues). As a result, positive samples include 2,811 interaction sites, whereas negative samples have 24614 noninterface residues.

The unbalanced sample size will cause overfitting of the sample with a large proportion; that is, the prediction is biased toward a classification with a larger number of samples, which will reduce the applicability of the model. The processing method at the data level is sampling. Undersampling, oversampling, and combined methods are three common and widely used approaches. Eight different methods from an unbalanced-learning library can be adopted to deal with the unbalanced data. These eight methods include SMOTE, ADASYN, BorderlineSMOTE, SVMSMOTE, ClusterCentroids, NearMiss, SMOTEENN, and SMOTETomek. The data sets processed by the above methods were subjected to the same subsequent experimental operations, so as to compare the results obtained by different processing methods, and to select a method that is more suitable for processing antioxidant proteins.

2.2. Feature Extraction. A wide range of characteristics was used in our experiment to classify protein interaction sites, including sequence features, secondary structure features, and 3D structural properties which are described as follows:

2.2.1. Sequence Feature

(1) Amino Acid Factors. Amino acids have several attributes, and there is a related database that has already organized and recorded the various attributes of amino acids, including physicochemical properties and biochemical properties [21]. AAIndex is a database that contains a quantitative index of numerous physicochemical and biological characteristics of amino acids. AAIndex was subjected to multivariable statistical analysis by Atchley et al. [22], which yielded five numeric attribute patterns: polarity, molecule volume, secondary structure, codon diversity, and electrostatic charge. These are the five numerical pattern scores used in this study. Each amino acid in a protein was encoded using these five amino acid parameters. Atchley factors are used to encode the physicochemical properties of amino acids. Each amino acid was represented by five Atchley factors, namely, polarity, codon diversity, secondary structure, molecular volume, and electrostatic charge. These five patterns or multidimensional indices were interpreted as follows: factor I = a complex index reflecting highly intercorrelated attributes for polarity, hydrophobicity, solvent accessibility, etc.; factor II = propensity to form various secondary structures, e.g., coil, turn, or bend versus alpha helix frequency; factor

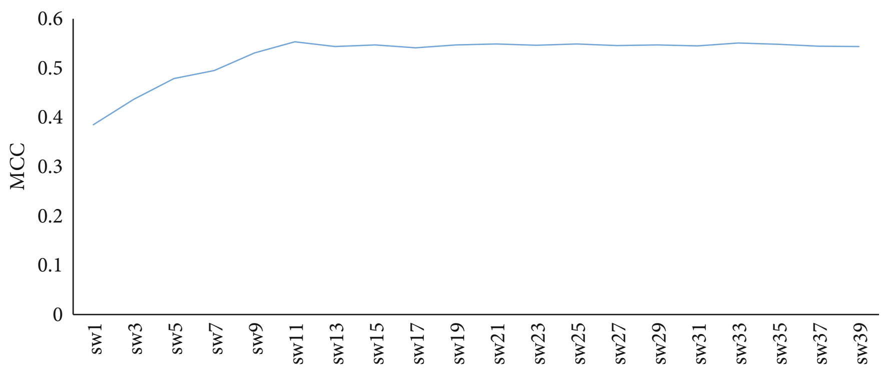

Figure 2: The prediction results with the feature space of the sliding window.

Table 2: For sliding windows of feature space prediction best results.

Dataset	Sensitivity	Specificity	Precision	Accuracy	MCC
SW11	0.463	0.974	0.824	0.870	0.553

III = molecular size or volume, including bulkiness, residue volume, average volume of a buried residue, side chain volume, and molecular weight; factor IV = relative amino acid composition in various proteins, number of codon coding for an amino acid, and amino acid composition; factor V = electrostatic charge including isoelectric point and net charge. A set of factor scores arising from these analyses provide a multidimensional index positioning each amino acid in these major interpretable patterns of physiochemical variation.

(2) PSSM Conservation Scores. Posttranslational modifications are common in the conservation protein regions, and that is why evolutionary conservation is vital for biological function. The position-specific score matrix (PSSM) was employed to measure the preservation of each amino acid in a protein sequence. For each residue, a 20D vector was utilized to represent the probability of conservation against mutations to 20 distinct amino acids. The position-specific scoring matrix (PSSM) [23] is a matrix composed of all such twenty-dimensional vectors for a particular peptide. PSSM conservation scores are obtained from position-specific iterative BLAST (PSI-BLAST) with parameters $j = 3$ and $h = 0.001$. Moreover, the alignment database is Swisspro [24].

2.2.2. Secondary Structure Feature

(1) Secondary Structure. The secondary structure of the relevant residues may impact the protein structures that play critical roles in protein function and the posttranslational modifications of certain residues [24]. In this study, we also employed solvent accessibility and secondary structure to encode each peptide in our investigation. The predictor SSpro4 [25] predicted solvent accessibility and secondary structure [26]. SSpro4 data was encoded using the letters 'E' for strand, 'H' for helix, and 'C' for other. A 3D binary vector was used to convert these words into numeric vectors: 100, 010, and 001, respectively. Because buried residues are never present in a protein interface, we deleted all peptides in all samples that were centered on a predicted buried residue.

(1) Disorder Score. Interaction sites, which are critical loci for numerous protein-protein interactions like methylation and phosphorylation, are frequently abundant in intrinsic disorder areas. As a result, such areas are crucial for protein structure and function [27]. As a consequence, we encoded the peptides using the structural disorder of the residues in the sequence. VSL2, which can reliably predict both short and long disordered areas in proteins, was used to compute a disorder score for each residue in a given protein sequence [28].

2.2.3. 3D Structural Features. The method of using the 3D structural feature plays an important role in promoting the effects of PPI site prediction [29]. We also employed this method in our study; based on the work of Sikic et al. [10], we selected 7 different features, namely, ASA, RASA, DPX, CX, AS, and SC, as well as another feature named Hydrophobicity. We used the program Protein structure and Interaction Analyzer (PSAIA) and the program Surface Racer [18] to fetch these 3D architectural features from the PDB database.

(1) Features from PSAIA. PSAIA is a program that calculates geometric parameters for a large number of protein structures to anticipate and explore protein-protein interaction sites [30]. It is possible to determine the following geometry parameters: The Kyte and Doolittle scale assigns a hydrophobicity value to each residue [31, 32].

(2) Features from Surface Racer. Research has shown that the way components of the large molecular surface interact with solvent and tiny solutes in solution determines protein stability and solubility [33]. As a result, one of the most critical factors in determining the structure of large molecules and their function is the macromolecular surface. In this study, we also took into account Molecular Surface Area and Surface Curvature. Program Surface Racer has estimated these characteristics based on the PDB database. These features were predicted by Program Surface Racer from the PDB database.

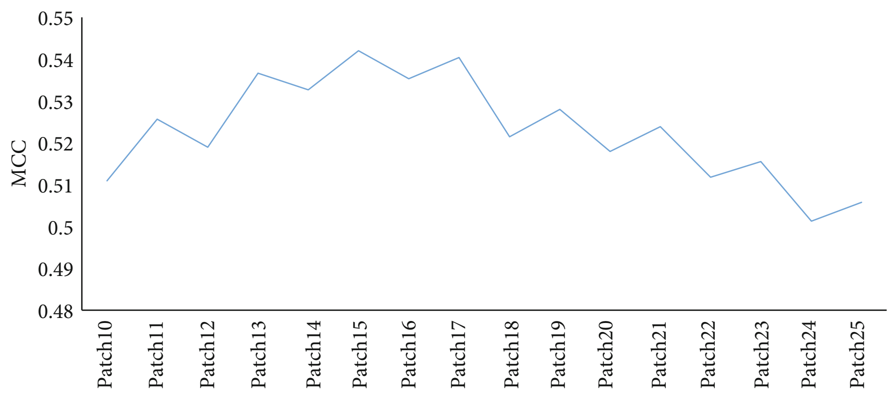

Figure 3: The prediction results with the feature space of the patch.

Table 3: For a patch of feature space prediction best results.

Dataset	Sensitivity	Specificity	Precision	Accuracy	MCC
Patch15	0.471	0.968	0.793	0.866	0.542

Table 4: The ideal results compared from single residue, sliding window, and patch.

Dataset	Sensitivity	Specificity	Precision	Accuracy	MCC
Single	0.267	0.980	0.778	0.835	0.390
SW11	0.463	0.974	0.824	0.870	0.553
Patch15	0.471	0.968	0.793	0.866	0.542

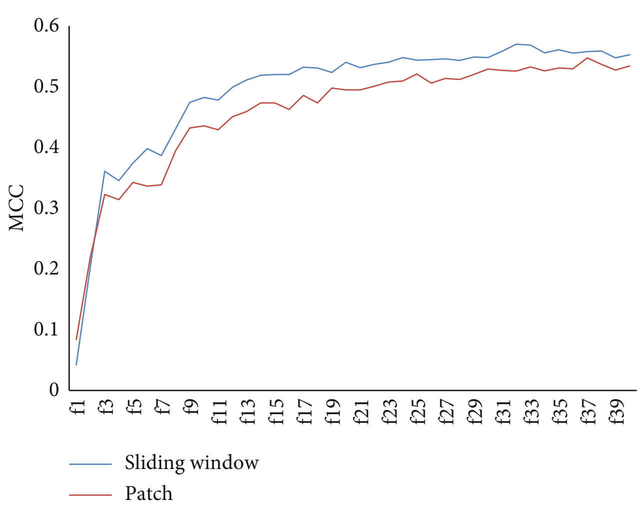

Figure 4: Sliding window and patch mRMR results.

Table 5: Sliding window and patch IFS result.

Dataset	Sensitivity	Specificity	Precision	Accuracy	MCC
SW11_32	0.480	0.975	0.833	0.874	0.570
Patch15_37	0.449	0.977	0.831	0.869	0.547

2.3. The Feature Space. We used 40 features for each residue in a protein segment, including 5 amino acid factor features, 20 PSSM conservation score features, 3 secondary structure features, 1 disorder feature, and 11 3D structural features from the PDB data.

In this study, we use three different kinds of ways to build feature space. Firstly, we use a single residue. Secondly, using window sliding, we were able to obtain N-residue protein segments centered on the indicated PPI residue, with n residues upstream and n residues downstream of the interaction site. For the peptides with lengths less than N amino acid residues, we complemented it with "X", where $1 \le n \le 19$, and $N = 2n + 1$. Thirdly, we extracted a patch-based model to characterize every residue. Each patch was made up of a center residue and its $m - 1$ nearest spatial residues, where $10 \le m \le 25$. The nonsurface residues are ignored in the present study, which solely deals with surface residues.

2.4. mRMR Method. To value the importance of each feature, we employed the mRMR technique [34]. The mRMR technique grades features based on their association to the target as well as feature redundancy. Mutual information (MI), which estimates the degree to which one vector is connected to another, was used to quantify both relevance and redundancy. The MI can be expressed using

$$I(x, y) = \sum_{i,j} p\left(x_i, y_j\right) \log \frac{p\left(x_i, y_j\right)}{p(x_i)p\left(y_j\right)}, \tag{1}$$

where x and y represent the two random vectors, $p(x)$ and $p(y)$ are the marginal probabilistic densities, and $p(x_i, y_j)$ is the joint probabilistic density. Mutual information can well describe the selected features and the relationship between the output categories. If the output category has selected features and mutual information, the more evidence that the characteristics comprise information categorization, the more effective it will be for classification and recognition [7]. We can select contribution to feature subset categorization by computing mutual information between the characteristics and the type and characteristics. The bigger the redundancy, the better the characteristic. The smaller the correlation, the better the feature will be represented. We

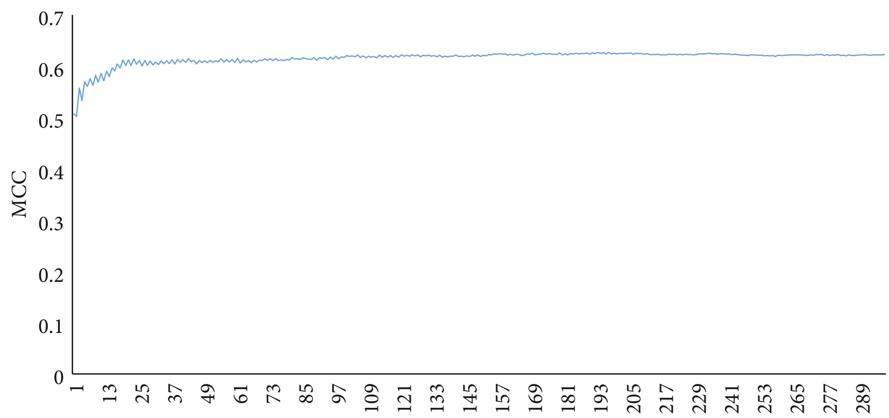

FIGURE 5: The influence of TREE number on the result.

TABLE 6: The influence of the TREE number on the result.

Dataset	Sensitivity	Specificity	Precision	Accuracy	MCC
Default trees	0.498	0.975	0.838	0.878	0.584
197_trees	0.550	0.976	0.854	0.889	0.627

determined that we could extract data from the results using the MIQ approach. We assume that the set K_m is the existing selected feature set composed of m features, and the set K_n is the feature set to be selected having n features.

$$D = I(f, c), \tag{2}$$

where D is the association between the feature f in K_m and the class c, and R is the association between the feature f in S_m and all features in S_n, and R can be calculated by

$$R = \frac{1}{m} \sum_{f i \in K_m} I(f, f_i). \tag{3}$$

So the feature f_i in the set K_n can be calculated as

$$\max_{f_j \in K_n} \left[I\left(f_j, c\right) - \frac{1}{m} \sum_{f_i \in M} I\left(f_j, f_i\right) \right], \quad (j = 1, 2, \cdots, n). \tag{4}$$

In this work, we used the mRMR program which is publicly available at http://penglab.janelia.org/proj/mRMR/.

2.5. Random Forest. In this study, RF was used as the prediction engine, and the default settings were used. An RF is an ensemble predictor composed of several decision trees. A new query sample coded by an input vector is placed into each of the forest's trees to classify it. A projected class is provided by each decision tree [35]. The class with the most votes will be chosen as the random forest's anticipated class.

In this work, we employed the RF program embedded in the Weka package for classification, and the Weka package is openly available at http://www.cs.waikato.ac.nz/ml/weka/index_downloading.html.

2.6. Incremental Feature Selection. Based on the data list, we selected the optimal characteristic set with IFS. It ranks each eigenvalue on the list by scores from high to low. Moreover, every single time we chose the first $i(1 \le i \le 40)$ with feature concentration as feature subset. We derived consequences with the RF classifier; eventually, we obtained 40 feature subsets with 40 prediction results and selected the character subset with the highest value of MCC as the optimal feature subset.

$$F = \left\{ f'_1, f'_2, f'_3, \cdots, f'_i \right\}. \tag{5}$$

2.7. Prediction Engine and Assessment. We used 10 cross-validation and different evaluation metrics to assess each predictor's performance. The evaluation metrics included sensitivity, precision, specificity, accuracy, and MCC (Mathews correlation coefficient) were used. These measures were calculated as shown below:

$$\begin{cases} \text{sensitivity} = \dfrac{\text{TP}}{\text{TPN}} \text{where TPN} = \text{TP} + \text{FN} \\ \text{precision} = \dfrac{\text{TP}}{\text{TFP}} \text{where TFP} = \text{TP} + \text{FP} \\ \text{specificity} = \dfrac{\text{TN}}{\text{TN} + \text{FP}} \\ \text{accuracy} = \dfrac{\text{TP} + \text{TN}}{\text{TP} + \text{TN} + \text{FP} + \text{FN}} \\ \text{MCC} = \dfrac{\text{TP} * \text{TN} - \text{FP} * \text{FN}}{\sqrt{(\text{TP} + \text{FP})(\text{TP} + \text{FN})(\text{TN} + \text{FP})(\text{TN} + \text{FN})}}, \end{cases} \tag{6}$$

where TP denotes true positive, TN denotes true negative, FP denotes false positive, and FN denotes false negative.

3. Results and Discussion

3.1. Performance Evaluation on Different Feature Space Methods. In this study, we used three kinds of the classical method of constructing feature space, namely, single residue, nonoverlapping sliding window, and overlapped patch-

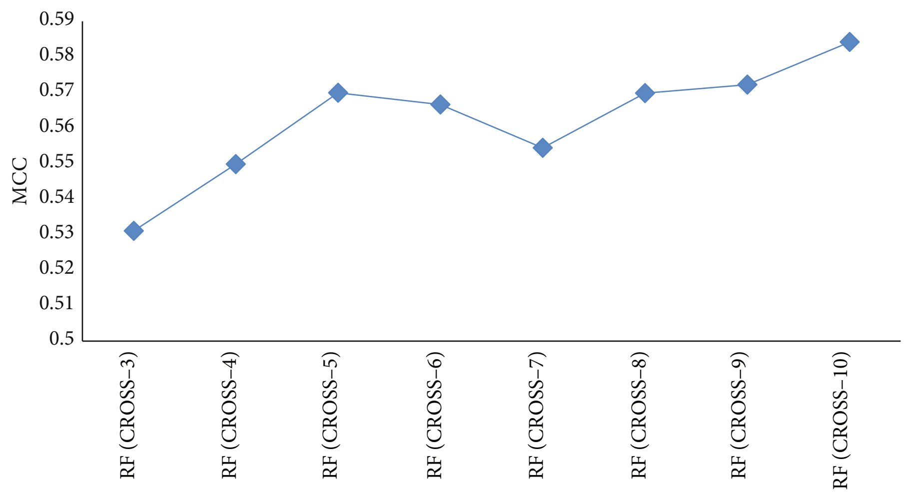

FIGURE 6: The influence of cross-validation adjustment on the result.

TABLE 7: The influence of cross-validation adjustment on the result.

Dataset	Sensitivity	Specificity	Precision	Accuracy	MCC
10-fold cross-validation	0.551	0.976	0.855	0.877	0.636

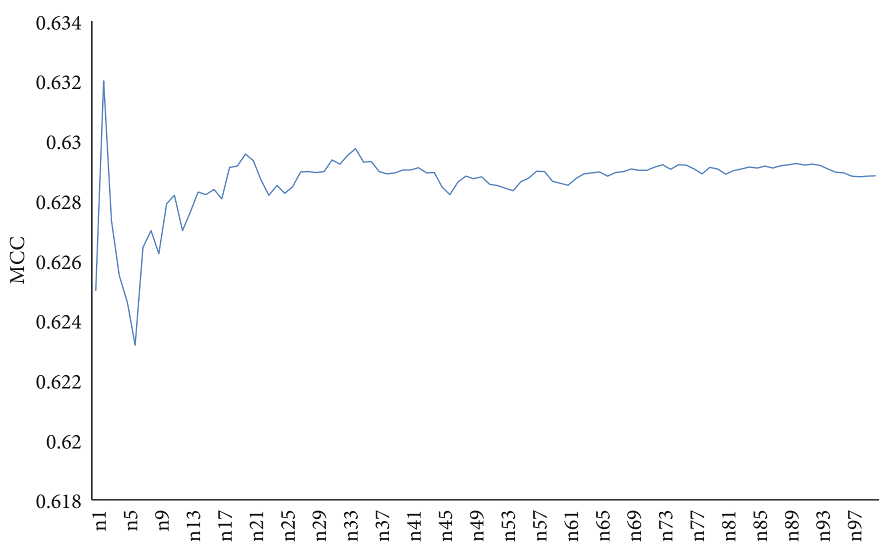

FIGURE 7: The results of 100 times the average.

TABLE 8: The results over imbalanced and trimmed data.

Dataset	Sensitivity	Specificity	Precision	Accuracy	MCC
Imbalanced	0.551	0.976	0.855	0.877	0.636
Trimmed	0.822	0.807	0.810	0.814	0.667

based method, on the spatial structure. We compared all three methods using three machine learning models. The prediction result of the single residue of feature space is shown in Table 1.

We can see that the predicting outcomes are with lower accuracy and sensitivity but higher specificity. It shows that the problem of the distinctiveness of feature from the feature space of the single residue has not been well addressed. The second way to build feature space is based on the sequence of sliding window, window length $N = 2n + 1 (1 \le n \le 19)$. The prediction results are shown in Figure 2.

It can be observed that the curve shows an upward trend and the overall curve is smooth. When the length of the sliding window increased, the prediction results are better. When the window length is stable at 11, the curve is smooth. When the length is 11, it reaches the maximum value based on the method of the sliding window. For a window of length 11, the results of the evaluation index t are as shown in Table 2. The sensitivity, precision, specificity, accuracy,

Table 9: Performance comparison with other methods.

Methods	Sensitivity	Specificity	Accuracy	MCC
Wang et al. [8]	0.698	0.666	0.729	0.230
Nguyen and Rajapakse [27]	0.436	0.926	0.803	0.349
Ofran and Rost [6]	0.763	0.786	0.863	0.376
Proposed method	0.822	0.807	0.814	0.667

and MCC obtained are 0.463, 0.834, 0.974, 0.870, and 0.553, respectively.

The third way to build feature space is using the patch-based method. We extracted a patch-based model to characterize every residue. Each patch was made up of a center residue and its $m-1$ nearest spatial residues, $10 \leq m \leq 25$. The prediction results are shown in Figure 3.

We can see from Figure 3 that the curve is overall steeper and presents a rising tendency, and when the number of residues in the patch increased, the prediction results are better. When we take the number of residue from the patch with 15, the MCC reaches its maximum value. Based on the method of the patch, we take the window length with 15 and take this outcome as the result of this method (as shown in Table 3). The sensitivity, precision, specificity, accuracy, and MCC obtained are 0.471, 0.793, 0.968, 0.866, and 0.542, respectively.

To provide a comprehensive analysis of the three methods, Table 4 shows the comparative results of the three methods in terms of sensitivity, specificity, accuracy, and MCC.

Based on the results of the 3 methods, it is evident that the predicted outcomes of sliding windows and patch methods are ideal than the single residue. Hence, this study employed the method of the patch and sliding windows to predict the results.

3.2. Performance Evaluation with Different Parameters. Figure 4 shows the prediction results when the features are selected using mRMR. Out of all features, 40 features were selected using mRMR. Two methods of feature space were employed, namely, the sliding window and patch-based feature space method. For the sliding window, the length of the sliding window was set to 11, and for the patch-based method, 15 is used.

We have separately established 40 feature subsets for window size 11 and patch 15 with the method of IFS and then obtained the prediction results as shown in Figure 4. The increasing tendency is obvious when we take the number of features from 1 to 9, then the curve tends to smooth and the MCC reaches its maximum value when the number of the features is 32. Similarly, the increasing tendency is obvious when we choose the number of features from 1 to 11, then the curve tends to smooth and the MCC reaches its maximum value when the number of the features is 37. The value of sensitivity, precision, specificity, accuracy, and MCC reported are 0.449, 0.831, 0.977, 0.869, and 0.547, respectively. The comparative results of the sliding window with patch ways show that the sliding window has more exact results than a patch.

We can conclude from Table 5 that the value from the optimal feature subset with window size 11 is higher than the MCC and sensitivity of patch 15.

3.3. Performance with Different RF Parameters. The RF (retention factor) is defined as the migration distance of the protein through the gel divided by the migration distance of the dye front [36]. The distance should be measured from the top of the resolving gel to the band of interest. An RF value is the distance in millimeters the amino acid traveled over the distance that the solvent traveled in millimeters. The RF values in thin layer chromatography are affected by the absorbent, the solvent, the chromatography plate itself, the application technique, and the temperature of the solvent and plate [37].

The default parameters of the random forest were used along with 10-fold cross-validation. To achieve optimized results, we repeat the experiment many times for each parameter and select the optimal result. Figure 5 shows the results for different tree numbers. It can be observed that with an increase in the number of RF trees, the MCC values increase from 1 to 27. After number 27, the line becomes straight.

To focus on both efficiency and accuracy, we selected the 197 fattest trees as samples and generated the results. The sensitivity, precision, specificity, accuracy, and MCC obtained are 0.553, 0.839, 0.973, 0.887, and 0.621, respectively, as shown in Table 6.

Figure 6 shows the results of cross-validation. We have selected different numbers of folds including 3 to 10. All the MCC values show an upward trend; therefore, we employed the 10-fold cross-valuation, and the sensitivity, specificity, precision, accuracy, and MCC obtained are 0.551, 0.976, 0.855, 0.877, and 0.636, respectively (Table 7).

In this study, a total of 2,811 interaction sites are obtained as positive samples and 24614 noninterface residues are defined as negative samples. Positive samples are far less than negative samples; it will affect the result of prediction. To eliminate the imbalance of the positive and negative samples, we selected the same number of negative as positive samples repeatedly and combined them as individual subdatasets, and then the average results are taken as the last prediction results.

Figure 7 shows that the MCC scores obtained from random sampling for a hundred times and the sensitivity, precision, specificity, accuracy, and MCC reported are 0.822, 0.81, 0.807, 0.814, and 0.667, respectively. To verify the effectiveness of disposing unbalanced sample data, we compared the prediction results of the raw data and processed unbalanced sample data, as shown in Table 8.

From the above table, we can see that compared with the raw data the sensitivity of the processed balanced sample data has increased significantly. Sensitivity plays an important in evaluating the prediction results. MCC is a general index, from the omnibus MCC index that shows balanced number data set can get the highest MCC number. Therefore, we can conclude that the result of this paper is effective.

3.4. Performance Comparison with Existing Predictors. In previous studies, some researchers predicted interaction sites only from a single feature and method of constructing the single feature space rather than the ways used in our experiments [38, 39]. To further evaluate the effectiveness of the prediction method in this work, three additional experiments are implemented to predict interaction sites by utilizing the methods of Wang et al.'s [8], Nguyen and Rajapakse's [27], Ofran and Rost's [6] studies and the present study. The results of the four experiments are reported in Table 9.

It clearly shows that the performance of the proposed method outperforms the other three methods especially in terms of sensitivity and the MCC values. Since higher sensitivity means a better prediction in positive classes, it is very useful for correcting the identification of interface residues. The MCC value represents the composite index; the higher the MCC value, the better the overall performance of the predictor. This validates that the approach presented in this study is competent to the PPI sites.

4. Conclusion

Proteins play a crucial role in cell life activities, particularly in terms of predicting protein interaction sites, which allows us to get a better understanding of protein function and molecular recognition. This study established a new approach for predicting PPI sites and employed three distinct types of feature collection methods including sequence signatures, secondary structure feature, and 3D structural features. In addition, the model is designed with three features at the same time to evaluate the sliding window and patch methods based on the same public datasets. Within the PPI area, the proposed technique examines not only the physical properties of each amino acid but also sequence conservation information and residue disorder status. The PDB dataset is used to analyze solvent accessibility, secondary structure, and 3D structural properties. It also demonstrates that the sliding window classification accuracy is greater than the patch-based feature space method. In the proposed method, 32 characteristics were employed and an MCC value of 62.88% was achieved. The experiments results show that the proposed method is effective in addressing the problem of predicting the protein interaction site.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors do not have any possible conflicts of interest.

References

[1] R. Nowak, "Entering the postgenome era," *Science*, vol. 270, no. 5235, pp. 368-369, 1995.

[2] B. T. Chait, "Trawling for proteins in the post-genomeera-Trawling for proteins in the post-genome era," *Nature Biotech*, vol. 14, no. 11, p. 1544, 1996.

[3] B. D. Alberts, J. Lewis, M. Raff, K. Roberts, and J. D. Watson, *Molecular Biology of the Cell New York*, Garland, 1989.

[4] D. Vries and A. M. Bonvin, "How proteins get in touch: interface prediction in the study of biomolecular complexes," *Current Protein & Peptide Science*, vol. 9, no. 4, pp. 394–406, 2008.

[5] X. Gallet, B. Charloteaux, A. Thomas, and R. Brasseur, "A fast method to predict protein interaction sites from sequences[1]," *Journal of Molecular Biology*, vol. 302, no. 4, pp. 917–926, 2000.

[6] Y. Ofran and B. Rost, "Predicted protein-protein interaction sites from local sequence information," *FEBS Letters*, vol. 544, no. 1-3, pp. 236–239, 2003.

[7] H. X. Zhou and Y. Shan, "Prediction of protein interaction sites from sequence profile and residue neighbor list," *Proteins*, vol. 44, no. 3, pp. 336–343, 2001.

[8] B. Wang, P. Chen, D. S. Huang, T. L. Li, T.-M. Lok, and M. R. Lyu, "Predicting protein interaction sites from residue spatial sequence profile and evolution rate," *FEBS Letters*, vol. 580, no. 2, pp. 380–384, 2006.

[9] A. S. Aytuna, A. Gursoy, and O. Keskin, "Prediction of protein-protein interactions by combining structure and sequence conservation in protein interfaces," *Bioinformatics*, vol. 21, no. 12, pp. 2850–2855, 2005.

[10] M. Sikic, S. Tomic, and K. Vlahovicek, "Prediction of protein-protein interaction sites in sequences and 3D structures by random forests," *PLoS Computational Biology*, vol. 5, no. 1, article e1000278, 2009.

[11] N. Li, Z. Sun, and F. Jiang, "Prediction of protein-protein binding site by using core interface residue and support vector machine," *BMC Bioinformatics*, vol. 9, no. 1, 2008.

[12] J. R. Bradford, C. J. Needham, A. J. Bulpitt, and D. R. Westhead, "Insights into protein-protein interfaces using a Bayesian network prediction method," *Journal of Molecular Biology*, vol. 362, no. 2, pp. 365–386, 2006.

[13] A. Koike and T. Takagi, "Prediction of protein-protein interaction sites using support vector machines," *Protein Engineering, Design & Selection*, vol. 17, no. 2, pp. 165–173, 2004.

[14] I. Res, I. Mihalek, and O. Lichtarge, "An evolution-based classifier for prediction of protein interfaces without using protein structures," *Bioinformatics*, vol. 21, no. 10, pp. 2496–2501, 2005.

[15] Y. Ofran and B. Rost, "ISIS: Interaction sites identified from sequence," *Bioinformatics*, vol. 23, no. 2, pp. e13–e16, 2007.

[16] C. Yan, D. Dobbs, and V. Honavar, "A two-stage classifier for identification of protein-protein interface residues," *Bioinformatics*, vol. 20, Supplement 1, pp. i371–i378, 2004.

[17] S. Jones and M. Thornton, "Prediction of protein-protein interaction sites using patch analysis 1 1Edited by G.von Heijne," *Journal of Molecular Biology*, vol. 272, no. 1, pp. 133–143, 1997.

[18] J. R. Bradford and D. R. Westhead, “Improved prediction of protein-protein binding sites using a support vector machines approach,” *Bioinformatics*, vol. 21, no. 8, pp. 1487–1494, 2005.

[19] D. J. Zea, A. M. Monzon, G. Parisi, and C. Marino-Buslje, “How is structural divergence related to evolutionary information?,” *Molecular Phylogenetics and Evolution*, vol. 127, pp. 859–866, 2018.

[20] Y. Pan, S. Zhou, and J. Guan, “Computationally identifying hot spots in protein-DNA binding interfaces using an ensemble approach,” *BMC Bioinformatics*, vol. 21, no. S13, 2020.

[21] N. J. Burgoyne and R. M. Jackson, “Predicting protein interaction sites: binding hot-spots in protein-protein and protein-ligand interfaces,” *Bioinformatics*, vol. 22, no. 11, pp. 1335–1342, 2006.

[22] W. R. Atchley, A. D. Fernandes, T. Drüke, and J. Zhao, “Solving the protein sequence metric problem,” *Proceedings of the National Academy of Sciences*, vol. 102, no. 18, pp. 6395–6400, 2005.

[23] P. Fariselli, F. Pazos, A. Valencia, and R. Casadio, “Prediction of protein-protein interaction sites in heterocomplexes with neural networks,” *European Journal of Biochemistry*, vol. 269, no. 5, pp. 1356–1361, 2002.

[24] H. Neuvirth, R. Raz, and G. Schreiber, “ProMate: a structure based prediction program to identify the location of protein-protein binding sites,” *Journal of Molecular Biology*, vol. 338, no. 1, pp. 181–199, 2004.

[25] P. Farisellil, A. Zauli, I. Rossi, M. Finell, P. Martelli, and R. Casadio, “A neural network method to improve prediction of protein-protein interaction sites in heterocomplexes,” in *2003 IEEE XIII Workshop on Neural Networks for Signal Processing (IEEE Cat. No.03TH8718)*, pp. 33–41, Toulouse, France, 2003.

[26] J. Chung, W. Wang, and P. E. Bourne, “Exploiting sequence and structure homologs to identify protein-protein binding sites,” *Proteins*, vol. 62, no. 3, pp. 630–640, 2006.

[27] M. N. Nguyen and J. C. Rajapakse, “Protein-protein interface residue prediction with SVM using evolutionary profiles and accessible surface areas,” in *2006 IEEE Symposium on Computational Intelligence and Bioinformatics and Computational Biology*, Toronto, ON, Canada, 2006.

[28] J. S. Bernardes, J. H. Fernandez, and A. T. R. Vasconcelos, “Structural descriptor database: a new tool for sequence-based functional site prediction,” *BMC Bioinformatics*, vol. 9, no. 1, p. 492, 2008.

[29] M. H. Li, L. Lin, X. L. Wang, and T. Liu, “Protein-protein interaction site prediction based on conditional random fields,” *Bioinformatics*, vol. 23, no. 5, pp. 597–604, 2007.

[30] H. M. Berman, J. Westbrook, Z. Feng et al., “The Protein Data Bank,” *Nucleic Acids Research*, vol. 28, no. 1, pp. 235–242, 2000.

[31] W. Kabsch and C. Sander, “Dictionary of protein secondary structure: pattern recognition of hydrogen- bonded and geometrical features,” *Biopolymers*, vol. 22, no. 12, pp. 2577–2637, 1983.

[32] S. Kawashima and M. Kanehisa, “AAindex: Amino Acid index database,” *Nucleic Acids Research*, vol. 28, no. 1, p. 374, 2000.

[33] S. F. Altschul, T. L. Madden, A. A. Schäffer et al., “Gapped BLAST and PSI-BLAST: a new generation of protein database search programs,” *Nucleic Acids Research*, vol. 25, no. 17, pp. 3389–3402, 1997.

[34] J. Cheng, A. Z. Randall, M. J. Sweredoski, and P. Baldi, “SCRATCH: a protein structure and structural feature prediction server,” *Nucleic Acids Research*, vol. 33, no. Web Server, pp. W72–W76, 2005.

[35] J. Hoskins, S. Lovell, and T. L. Blundell, “An algorithm for predicting protein-protein interaction sites: abnormally exposed amino acid residues and secondary structure elements,” *Protein Science*, vol. 15, no. 5, pp. 1017–1029, 2006.

[36] H. Li, Y. Pang, B. Liu, and L. Yu, “MoRF-FUNCpred: molecular recognition feature function prediction based on multi-label learning and ensemble learning,” *Frontiers in Pharmacology*, vol. 13, 2022.

[37] Y. T. Shao, X. X. Liu, Z. Lu, and K. C. Chou, “pLoc_deep-mHum: predict subcellular localization of human proteins by deep learning,” *Natural Science*, vol. 12, no. 7, pp. 526–551, 2020.

[38] S. Jiao, L. Xu, and Y. Ju, “CWLy-RF: a novel approach for identifying cell wall lyases based on random forest classifier,” *Genomics*, vol. 113, no. 5, pp. 2919–2924, 2021.

[39] Q. Zhang, P. Liu, X. Wang, Y. Zhang, Y. Han, and B. Yu, “StackPDB: predicting DNA-binding proteins based on XGB-RFE feature optimization and stacked ensemble classifier,” *Applied Soft Computing*, vol. 99, article 106921, 2021.

Hindawi
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Retraction

Retracted: Senkyunolide H Affects Cerebral Ischemic Injury through Regulation on Autophagy of Neuronal Cells Via P13K/AKT/mTOR Signaling Pathway

Disease Markers

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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) Peer-review manipulation

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.

References

[1] B. Zhao, K. Tang, Y. Zhao, and W. Zhao, "Senkyunolide H Affects Cerebral Ischemic Injury through Regulation on Autophagy of Neuronal Cells Via P13K/AKT/mTOR Signaling Pathway," *Disease Markers*, vol. 2022, Article ID 9211621, 8 pages, 2022.

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Research Article

Senkyunolide H Affects Cerebral Ischemic Injury through Regulation on Autophagy of Neuronal Cells via P13K/AKT/mTOR Signaling Pathway

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Cerebral ischemia (CI) is associated with high global incidence and risk; therefore, its rapid and reliable therapeutic management is essential for protecting patients' lives and improving health. Senkyunolide H (SH) is remarkably effective against phlebosclerosis, oxidation, and apoptosis. Blood-brain barrier is the main obstacle impeding the delivery of drugs and xenobiotics to brain areas. Drugs' loading in nanoparticles can overcome the blood-brain barrier obstacle and thus directly and completely act on brain tissue, and such a loading can also change the half-life of drugs *in vivo* and lower the dosage requirement of drugs. In this study, we loaded the SH in lipid nanoparticles to improve its delivery to the brain for the therapy of CI. Thus, this study preliminarily analyzed the mechanism of SH-loaded nanoparticles in CI. The SH-loaded lipid nanoparticles were prepared and characterized with electron microscopy and PS potentiometery. The SH-loaded nanoparticles were intraperitoneally administered to CI-induced rats and brain tissue water content, and neuronal apoptosis and autophagy-associated proteins were determined. Our assays revealed SH-loaded nanoparticle's ability to reduce nerve injury and brain tissue water content in rats with CI and inhibit the apoptosis and autophagy of their neuronal cells (NCs). Additionally, under intervention with SH-loaded nanoparticles, P13K/AKT/mTOR pathway-associated proteins in brain tissue of rats decreased. As the assay results showed, SH-loaded nanoparticles can suppress the autophagy of NCs through medicating P13K/AKT/mTOR pathway and lower apoptosis, thus delivering the effect of treating CI. Results of this study indicate SH-loaded nanoparticles as promising strategy for delivery SH to brain areas for treating CI.

1. Introduction

Cardio-cerebrovascular diseases and chronic diseases with the highest global incidence are frequent among middle-aged and aged population [1]. Cerebral ischemia (CI) is a commonly occurring disease in elderly posing enormous threat to heath of the elder population [2]. Its occurrence is probably induced by atherosclerosis, hypertension, thrombosis, hyperlipidemia, diabetes, excitement, fatigue, and many others [3]. Without timely and effective therapy, CI might directly induce cerebral infarction, giving rise to irreversible neurological function deficit and even endanger patients' life and health in severe cases [4]. Currently, over 20 million new cases of CI are observed each year worldwide, and the number goes up annually as the global rate of elder population increases [5, 6]. Conservative therapy is preferred for the management of CI, where medicines are prescribed to the patients for a long run to control CI attack

[7]. For CI with multiple and complex inducements, effective plan to completely cure is still under investigation [8]. Thus, researchers are constantly searching to find out an efficient and effective way against CI [9].

Earlier studies have shown a strong link of CI with biological behavior changes of neuronal cells (NCs) many times [10, 11]. Autophagy, a physiological process of cell metabolism, plays a crucial role in the development of many diseases [12, 13]. Among cases with CI, autophagy of NCs can notably accelerate their apoptosis and thereby give rise to nerve tissue injury [14].

Ligusticum chuanxiong, a natural Chinese medicine component, is most frequently adopted as a medicine for promoting blood circulation and removing blood stasis [15]. Senkyunolide H (SH) is a typical phenolic compound found in Ligusticum chuanxiong. It has been shown to have remarkable effects against phlebosclerosis, oxidation, and apoptosis and in regulating inflammatory response [16]. However, during the development of CI, blood-brain barrier is highly prone to prevent the drug reaction from entering the brain tissue [17]. Loading drugs in nanoparticles are an advancement in the field of drug delivery where the drugs are converted to nanosized particles and improve its bioavailability. Drugs within nanoparticles with extremely small molecular structure and high activity as carriers can be delivered to various tissues and organs in the human body quickly [18]. In addition, nanoparticles can change the half-life of drugs *in vivo* and lower the dosage requirement of drugs [19]. Nanocarrier-based drugs have also been shown to traverse the blood-brain barrier and successfully deliver the loaded drug into brain areas. Therefore, we designed this study to prepare SH-loaded lipid nanoparticles and investigate its delivery to the brain for improving the current treatment status of CI and analyze its impact on CI and associated mechanisms, with the aim of offering novel reference of clinical therapy of CI.

2. Materials and Methods

2.1. Experimental Animal Data. Thirty Wistar rats (3-6 months old weighing 200-250 g) were purchased from Shanghai Medicilon Biopharmaceutical Co., Ltd. (animal license: SYXK (Shanghai) 2020-0038) and housed under 25°C and 40% humidity, with free access to light and drinking water. The study was conducted in Department of Neurology, Yongchuan Hospital of Chongqing Medical University, Chongqing, China. The flowchart of the study was shown in Figure 1.

2.2. Modeling Methods. The rats were randomly assigned to three groups. One group was kept as control and fed normally without any intervention, and the other two groups' animals were spared for CI modeling. Specifically, with reference to one study by Haji et al. [20], rats were anesthetized through intraperitoneal injection of 1% pentobarbital sodium (40 mg/kg), then immobilized in prone position, and routinely disinfected the head and hairs from the top of head that were removed. Then, a high-frequency electrotome was used for blocking the vertebral artery flow in left and right transverse foramina of the transverse process wings of the first cervical vertebra of each rat. After 24 h, the bilateral common carotid arteries were clamped by arterial clamp for 5 min. After modeling, rats with obvious confusion of consciousness, dilated pupils, shortness of breath, decreased pain, and no response of pupils to light source were regarded as successfully modeled.

2.3. Neurological Deficit Score (NDS) of Rats. The neurological function deficiency of the animals was assessed by an adopted scale where no signs: 0 points; inability of completely straightening the forelimb: 1 point; paralysis of one limb: 2 points; inability of standing up: 3 points; and no spontaneous activity: 4 points.

2.4. Detection of Brain Injury Markers. Blood from tail veins of the animals (0.5 mL) was subjected to 10 min centrifugation (1509 × g, 4°C) for serum collection, followed by determination of serum neuron-specific enolase (NES) and S-100β via enzyme linked immunosorbent assay (ELISA).

2.5. Preparation of SH-Loaded Nanoparticles. Dioleoyl lecithin (15 mg), cholesterol (5 mg), and distearate phosphatidylethanolamine-polyethylene glycol 2000 (15 mg) were dissolved in 30 mL chloroform and mixed thoroughly. Dioleoyl lecithin, cholesterol, distearate phosphatidylethanolamine-polyethylene glycol 2000, and chloroform were all purchased from Sigma-Aldrich via local supplier (the chemicals and solvents used in this study were of analytical grade and used as such without further purification). The organic solvent was removed by rotary evaporation (37°C) until dryness, and a film-like substance was formed on the base of the rotary flask. The film was dried for 12 h in a vacuum box, followed by addition of SH (15 mg) in 0.01 M preheated PBS. Finally, the mix was given 2 h centrifugation (500 × g, 37°C) and filtering via 0.22 μL filter membrane, followed by dying (4°C) to prepare SH-loaded nanoparticles.

2.6. Establishment of Standard Curve of SH-Loaded Nanoparticles. SH-loaded nanoparticles (1 mg) were dissolved in methanol (1 mL) and serially diluted to 2.5, 5, 10, 20, 30, and 40 μg/mL with methanol. The absorption of all the solutions was measured using the HPLC system (Shimadzu, Kyoto, Japan), and a standard curve was established.

2.7. Characterization of SH-Loaded Nanoparticles. The morphology of nanoparticles was observed under scanning electron microscope, and the particle size distribution was analyzed by nanosize potentiometer.

2.8. Intervention of SH-Loaded Nanoparticles on Rats with CI. Among the two groups of model rats, one group was intervened with SH-loaded nanoparticles as an SH group where the rats were administered 50 mg/kg SH-loaded nanoparticles 2 h after modeling. The other group was intervened with the same amount of normal saline as a model group (Mod group). Administration of both groups was completed within 24 h.

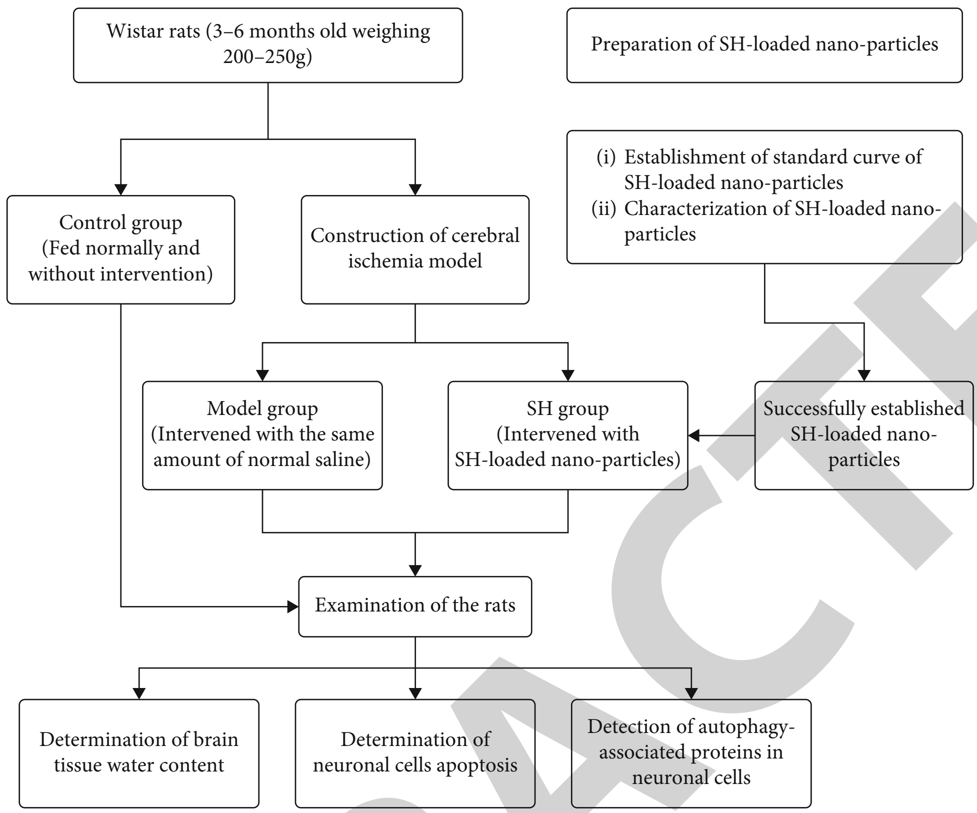


Figure 1: Flowchart of the presented study.

2.9. Determination of Brain Tissue Water Content (BTWC). The rats were euthanized by cervical dislocation under anesthesia, and their brains were taken and cut open along the coronal plane of the pinhole. A slice (approximate 3 mm thick) was taken in front of the pinhole, and the blood and cerebrospinal fluid were sucked off. The wet weight was measured by electronic balance. Then, the brain was subjected to 24 h drying (95°C) in an incubator, followed by measurement of dry weight. The water content in the brain tissue was determined by the formula below:

$$\text{Water content }(\%) = (\text{wet weight} - \text{dry weight})(\text{g})/\text{wet weight }(\text{g}) \times 100\% \tag{1}$$

2.10. Determination of Neuronal Apoptosis. Single-cell suspension (1×10^6 cells/mL) was prepared from brain tissue (30-50 mg), followed by 10 min reaction with 1 μL Annexin-V-FITC and 5 μL propidium iodid (PI) under dark environment and then addition of 400 μL buffer. Finally, flow cytometry was performed for determination of cell apoptosis.

2.11. Detection of Autophagy-Associated Proteins in NCs. Brain tissue of rats was lysed, followed by treatment with SDS-PAGE and transfer to a membrane. The tissue was overnight incubated (4°C) after being diluted with Tris-buffered saline with Tween-20 (0.1%) (TBST) to 1 : 1000 on a shaking bath. After being cleaned via TBST, second antibody was put in. One hour later, the gray value was evaluated via a BCA protein quantitative kit (Beyotime Biotechnology; Shanghai).

2.12. Statistical Analyses. SPSS (Version 22.0; IBM, US) was used for statistical analysis. Results were recorded as mean ± SD and analyzed via independent-samples t-test, one-way ANOVA, LSD test, repeated variance, or Bonferroni test. $P < 0.05$ was considered as statistically significant difference.

3. Results

3.1. Modeling Results of Rats with CI. Modeling results of rats with CI are shown in Figure 2. Figure 2(a) shows nerve defect score of the model rat with the control group representing that the model rats' nerve defect was statistically significant. Figure 2(b) shows serum neuron-specific enolase (NES) concentration of the model rat in comparison with the control group suggesting that the concentration of NES was high in the model rat group. Figure 2(c) depicts S-100β concentration of the model rat and control groups suggesting that S-100β concentration was high in the model rat group. The Mod group got a notable higher NDS than the control group (Con group) (2.87 ± 0.67) points vs. (1.00 ± 0.47) points, ($P < 0.05$, Figure 2(a)) and showed NES and S-100β of 22.68 ± 2.83 pg/mL and 242.15 ± 17.64 ng/mL, respectively, both notably higher than those in the Con group (both $P < 0.05$, Figures 2(b) and 2(c)).

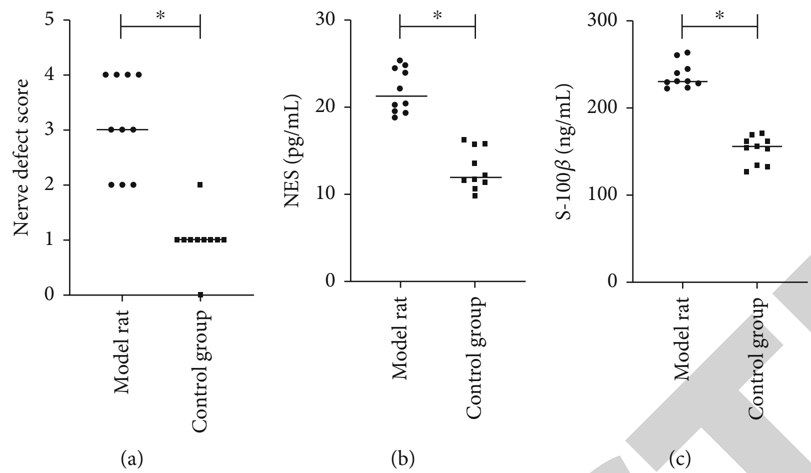


Figure 2: Modeling results. (a) Nerve defect score of the model group compared with the control group. (b) NES concentration of the model group compared with the control group. (c) S-100β concentration of the model group compared with the control group. * represents $P < 0.05$.

3.2. Preparation Results of SH-Loaded Nanoparticles. After determination of the peak areas under different concentrations of SH-loaded nanoparticle solutions, a standard curve of SH-loaded nanoparticles was constructed with drug concentration of SH-loaded nanoparticles as the ordinate and the peak area as the abscissa (Figures 3(a) and 3(b)).

3.3. Characterization of SH-Loaded Nanoparticles. Under the electron microscope, SH-loaded nanoparticles showed even distribution and densely round structure, with obvious substances in the gaps between the particles that might be free SH (Figure 4(a)), and indicated SH-loaded nanoparticles obtained good shape and size distribution uniformity with fewer impurity content. According to the PS spectrometer, the PS of SH-loaded nanoparticles was around 80-120 nm (Figure 4(b)).

3.4. Impact of SH-Loaded Nanoparticles on NDS of Rats. The SH group showed neurological deficit score (NDS) of (1.84 ± 0.52) points, lower than that of the Mod group, but higher than that of the Con group ($P < 0.05$, Figure 5).

3.5. Impact of SH-Loaded Nanoparticles on Nerve Injury. The SH group showed NES and S-100β concentrations of (15.63 ± 1.18) pg/mL and (192.66 ± 8.42) ng/mL, lower than those in the Mod group, but higher than those in the Con group (all $P < 0.05$, Figures 6(a) and 6(b)). Additionally, the SH group had BTWC of (74.33 ± 4.24) %, which was also lower than that of the Mod group, but higher than that of the Con group ($P < 0.05$, Figure 6(c)).

3.6. Impact of SH-Loaded Nanoparticles on Neuronal Apoptosis. Compared to the control group, the apoptosis rate in the model group was significantly increased; after SH-loaded nanoparticles intervention on rats with CI, the apoptosis rate was decreased. Bcl-2 and Bax are a pair of homologous genes regulating cell apoptosis. The high expression of Bcl-2 can inhibit the occurrence of cell apoptosis, and Bax can antagonize the antiapoptotic effect of Bcl-2 and play a role in accelerating cell apoptosis.The SH group showed higher protein expression of Bcl-2 and lower protein expression of Bax than the model group and the control group (all $P < 0.05$, Figures 7(a) and 7(b)).

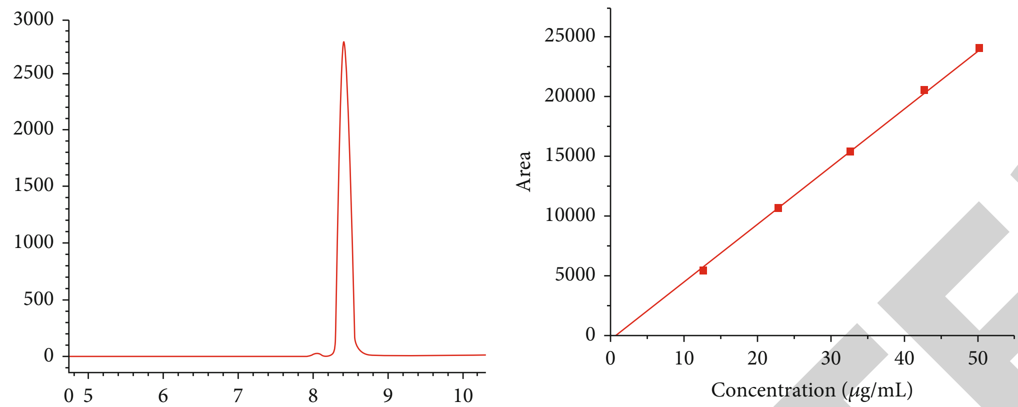
3.7. Impact of SH-Loaded Nanoparticles on Autophagy of NCs. The SH group had no difference in Beclin-1 and LC3 when compared with the control group but showed lower levels of Beclin-1 and LC3 when compared with the model group (all $P < 0.05$, Figure 8).

3.8. Impact of SH-Loaded Nanoparticles on P13K/AKT/mTOR Pathway. The SH group animals showed lower levels of P13K, AKT, and mTOR than the model group and higher levels of P13K, AKT, and mTOR when compared with the control group (all $P < 0.05$, Figure 9).

4. Discussion

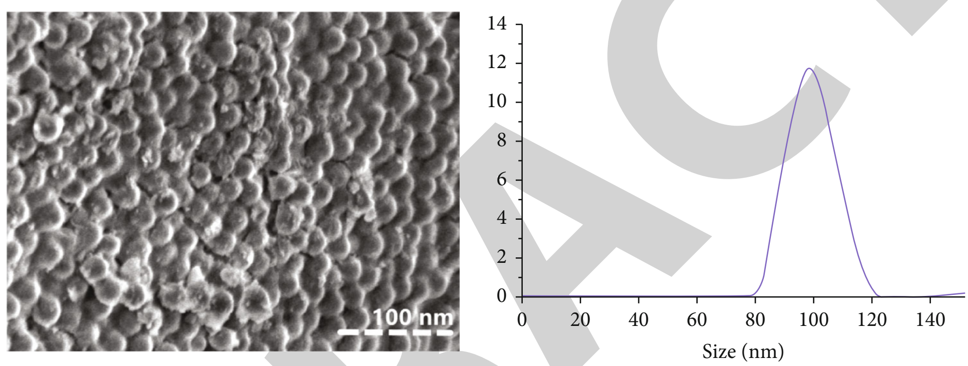
Over the past few years, an upsurge in the incidence of cerebral ischemia (CI) has been observed which is posing increasingly serious threat to public health [20]. It is a hotspot and challenge in modern clinical research to deeply understand the pathogenesis of CI and find a solution for treating it from molecular perspectives [21]. The protective effect of senkyunolide H on cranial nerve has been justified in previous studies [22], but its clinical application has far to go.

In this study, we have initially overcome the technical difficulties in the future clinical application of SH through nanotechnology, which may be a huge breakthrough in the clinical treatment of CI. Our study firstly established rat models with CI and compared the neurological deficit score and NES and S-100β between CI rats and normal control group. The results showed notably increased NDS and NES and S-100β in the model group, which fully verified the success of the modeling. Neurologic evaluation is not only an index to judge the success of the model but also provides a certain basis for the study of the pathophysiology, model standardization, and drug intervention. Neuron-specific enolase (NES), one enolase implicated in glycolytic pathway,



(a) (b)

Figure 3: Preparation results of SH-loaded nanoparticles. (a) Peak area of SH-loaded nanoparticles solutions. (b) Standard curve.



(a) (b)

Figure 4: Characterization of SH-loaded nanoparticles. (a) Morphology of SH-loaded nanoparticles visualized under electron microscope. (b) Size distribution of SH-loaded nanoparticles analyzed with PS potentiometer.

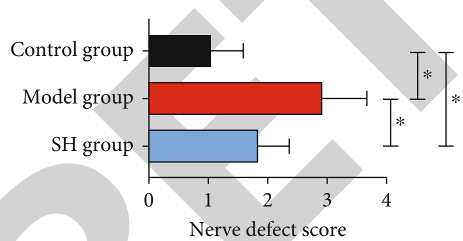


Figure 5: Impact of SH-loaded nanoparticles on NDS of rats compared with the model group and control group. * represents P value less than 0.05.

shows the highest activity in brain cells. When brain tissue is damaged, the permeability of tissues and blood vessels will increase, while NES will be released into other tissues in large quantities, causing a higher NES concentration [23]. S-100β is an acidic calcium-binding protein, with a high specific response to brain injury and a high association with nervous system diseases [24]. The responses of NES and S-100β to nerve injury have been verified in many previous studies [25, 26]. After determined the peak areas under different concentrations of SH-loaded nanoparticle solutions, the results showed that SH-loaded nanoparticles at 10-50 μg/mL had a good reaction effect, which is consistent with the study by Xiong et al. [27] on SH-loaded nanoparticles. Subsequently, we found the size of SH-loaded nanoparticles in the range of 80-120 nm, and that of brain capillary size is approximately 100 nm [28], which also confirms that SH loaded nanoparticles can directly act on brain tissue through brain capillary and blood-brain barrier, thus improving the drug use efficiency.

Then, we administered SH-loaded nanoparticles to the CI rats. As a result, the rats showed a decrease in NDS and NES and S-100β, which indicates that the nerve injury of rats with CI was alleviated greatly under the intervention of SH-loaded nanoparticles. Earlier studies have also demonstrated the good efficacy of SH on nervous system diseases such as glioma and migraine [29, 30]. It can be due to the following reasons: SH can suppress the induction process of the decrease of erythrocyte deformability index and orientation index by concanavalin A, during which the erythrocyte deformability declines, and it is thus unable to enter the brain tissue through capillaries for blood circulation, finally creating the situation for the first step of cerebral embolism [31]. Then, groups of red blood cells gather and pile up at the blood-brain barrier to form thrombus, which causes both ischemic injury and hypoxia reaction of brain

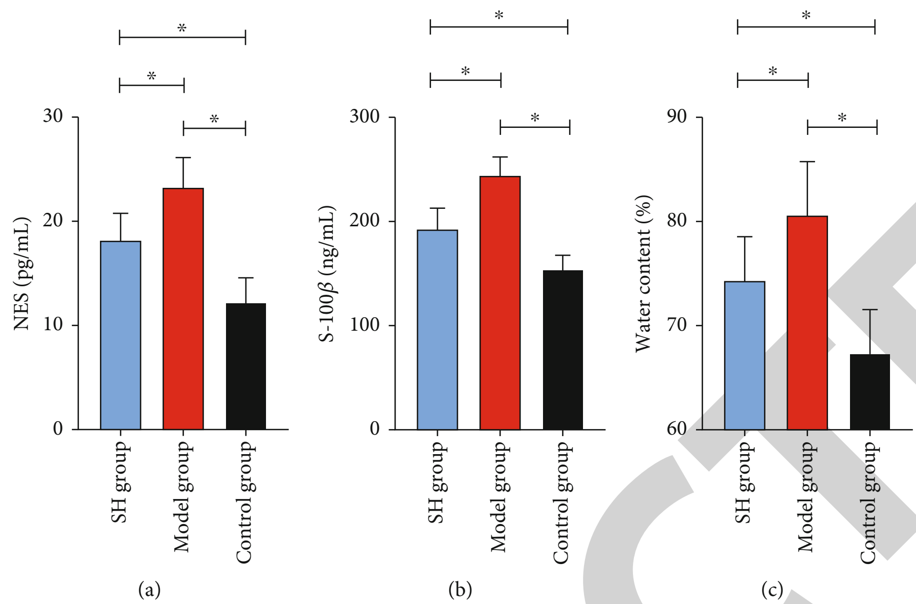


Figure 6: Impact of SH-loaded nanoparticles on nerve injury compared with the model group and control group. (a) NES concentration of the SH group compared with the model group and control group. (b) S-100β concentration of the SH group compared with the model group and control group. (c) BTWC of the SH group compared with the model group and control group. * represents P value<0.05.

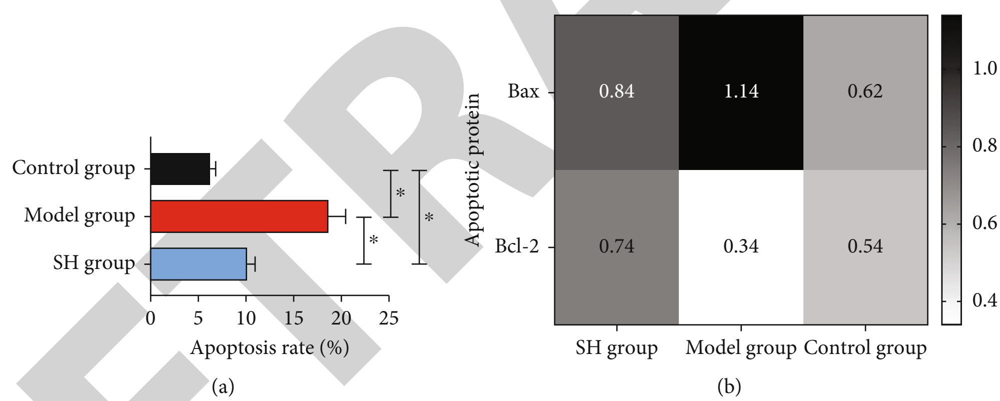


Figure 7: Impact of SH-loaded nanoparticles on neuronal apoptosis. (a) Neuronal apoptosis of the SH group compared with the model group and control group. (b) Bax and Bcl-2 proteins of the SH group compared with the model group and control group. $^*P < 0.05$.

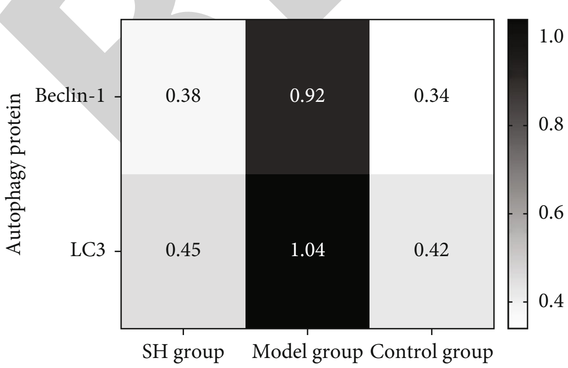


Figure 8: Impact of SH-loaded nanoparticles on autophagy of NCs compared with the control group and model group.

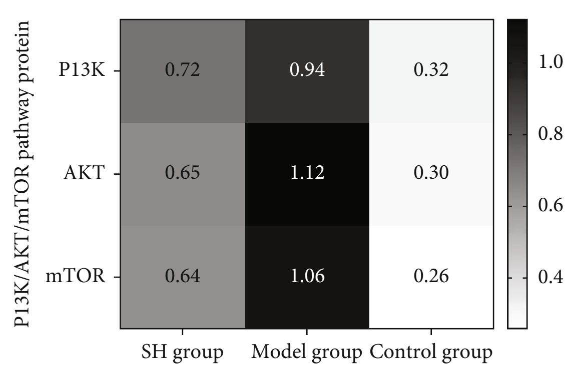


Figure 9: Impact of SH-loaded nanoparticles on P13K/AKT/mTOR pathway in the SH group compared with control and model groups.

tissue [32]. At the same time, the results of this study showed that the above results can be verified by comparing the brain water content of rats in each group. With the increase of blood-brain barrier permeability, capillary hypoxia edema and brain water content increased [33]. Therefore, the decrease of brain tissue water content indicates that SH has a strong effect on improving brain tissue microenvironment.

For further understanding the mechanism of SH on CI, we investigated the apoptosis and autophagy of neuronal cells (NCs) in the three groups. The results showed that the apoptosis and autophagy of NCs were obviously suppressed after SH intervened, suggesting that the impact of SH on CI might be due to regulation of autophagy of NCs. Beclin-1 and LC3, the most classical autophagy markers, increase with the increase of autophagy in cells [34]. It is precisely because of the acceleration of autophagy that the apoptosis of NCs increases; so, irreversible nerve injury is likely to occur during CI [35]. Moreover, according to one earlier study [36], SH can regulate autophagy of myocardial ischemic cells, which also verifies our results. Finally, we quantified P13K, AKT, and mTOR in brain tissue and found that under intervention with SH, all the three decreased, suggesting the inhibition of P13K/AKT/mTOR pathway. As a classic pathway, it is frequently studied in brain nerve injury diseases [37, 38]. It can mediate the activation of fibroblast growth factor, vascular endothelial growth factor, human growth factor, angiopoietin I, and other substances that stimulate blood and vascular activity and thus promote the development of thrombosis [39]. This study has confirmed that SH-loaded nanoparticles can impact NCs with CI through suppressing P13K/AKT/mTOR signaling pathway.

5. Conclusion

In this study, we loaded the SH in lipid nanoparticles and successfully obtained SH-loaded nanoparticles with 80-120 nm size in good shape and size distribution uniformity. The intervention of SH-loaded nanoparticles in CI rats can significantly alleviate the nerve injury of CI rats and decrease the apoptosis of the neuronal cells. Meanwhile, the SH-loaded nanoparticles could suppress the autophagy of NCs by medicating P13K/AKT/mTOR signaling pathway and lower apoptosis. Above all, SH-loaded nanoparticle can act as a promising strategy for delivery SH to brain areas, which can be an effective and promising method for treating CI.

Data Availability

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

Conflicts of Interest

The authors declare no competing interests.

Authors' Contributions

Bei Zhao, Ke-Cheng Tang, and Ying Zhao contributed equally to this work and are co-first authors. Wang Zhao designed and performed research. Bei Zhao, Ke-Cheng Tang, and Ying Zhao performed statistical analysis and wrote the manuscript. Bei Zhao, Ke-Cheng Tang, and Ying Zhao provided the materials and interpreted the data. Bei Zhao, Ke-Cheng Tang, and Ying Zhao collected and analyzed the data. All authors contributed to the article and approved the submitted version.

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References

[1] U. Lendahl, P. Nilsson, and C. Betsholtz, "Emerging links between cerebrovascular and neurodegenerative diseases—a special role for pericytes," *EMBO Reports*, vol. 20, no. 11, article e48070, 2019.

[2] O. A. Sveinsson, O. Kjartansson, and E. M. Valdimarsson, "Cerebral ischemia/infarction-epidemiology, causes and symptoms," *Læknablaðið*, vol. 100, no. 5, pp. 271–279, 2014.

[3] O. A. Sveinsson, O. Kjartansson, and E. M. Valdimarsson, "Cerebral ischemia/infarction-diagnosis and treatment," *Læknablaðið*, vol. 100, no. 7-8, pp. 393–401, 2014.

[4] Z. Yang, C. Weian, H. Susu, and W. Hanmin, "Protective effects of mangiferin on cerebral ischemia-reperfusion injury and its mechanisms," *European Journal of Pharmacology*, vol. 771, pp. 145–151, 2016.

[5] G.-C. Zhao, Y.-L. Yuan, F.-R. Chai, and F.-J. Ji, "Effect of *Melilotus officinalis* extract on the apoptosis of brain tissues by altering cerebral thrombosis and inflammatory mediators in acute cerebral ischemia," *Biomedicine & Pharmacotherapy*, vol. 89, pp. 1346–1352, 2017.

[6] A. Hasso, W. Stringer, and K. Brown, "Cerebral ischemia and infarction," *Neuroimaging Clinics of North America*, vol. 4, no. 4, pp. 733–752, 1994.

[7] P. Berlit, B. Endemann, and P. Vetter, "Zerebrale Ischämien bei jungen Erwachsenen," *Fortschritte der Neurologie-Psychiatrie*, vol. 59, no. 8, pp. 322–327, 1991.

[8] D. Ridder and M. Schwaninger, "Nf-κb signaling in cerebral ischemia," *Neuroscience*, vol. 158, no. 3, pp. 995–1006, 2009.

[9] C.-C. Chen, Y.-L. Wang, and C.-P. Chang, "Remarkable cell recovery from cerebral ischemia in rats using an adaptive escalator-based rehabilitation mechanism," *PLoS One*, vol. 14, no. 10, article e0223820, 2019.

[10] X. Zhang, H. Yan, Y. Yuan et al., "Cerebral ischemia-reperfusion-induced autophagy protects against neuronal injury by mitochondrial clearance," *Autophagy*, vol. 9, no. 9, pp. 1321–1333, 2013.

[11] Y. Liu, X. Xue, H. Zhang et al., "Neuronal-targeted tfeb rescues dysfunction of the autophagy-lysosomal pathway and alleviates ischemic injury in permanent cerebral ischemia," *Autophagy*, vol. 15, no. 3, pp. 493–509, 2019.

[12] C. Chen, H. Qin, J. Tan, Z. Hu, and L. Zeng, "The role of ubiquitin-proteasome pathway and autophagy-lysosome pathway in cerebral ischemia," *Oxidative Medicine and Cellular Longevity*, vol. 2020, Article ID 5457049, 12 pages, 2020.

[13] J. Jing, X. Liu, X. Geng et al., "Autophagy mechanism of cerebral ischemia injury and intervention of traditional Chinese