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New Strategies for High Quality of CPR and Post-Resuscitation Care

Lead Guest Editor: Yan-Ren Lin
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Editorial

New Strategies for High Quality of CPR and Post-Resuscitation Care

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Following cardiac arrest, establishing the return of spontaneous circulation (ROSC) and the neurological function of the patient is the key, and the quality of the cardiopulmonary resuscitation (CPR) has a direct effect on the protection of the central and distal vital organs. In addition to traditional chest compression, high-performance cardiopulmonary resuscitation (HPCPR) and extracorporeal cardiopulmonary resuscitation (ECPR) are thought to be associated with a healthier and higher optimal organ perfusion with minimal disruption. Unfortunately, the effect and the cost of these treatments should both be considered; therefore, the current recommendations are still evolving. Recently, the American Heart Association (AHA) published the "Cardiac Arrest and Cardiopulmonary Resuscitation Outcome Reports" on September 16, 2019. The Utstein-style reporting templates were revised, and certain "core variables" were considered essential for the quality improvement programs [1]. Moreover, the European Resuscitation Council (ERC) also pointed out the importance of the CPR quality (ECPR, ECLS, and mechanical CPR) in their 2020 guidelines [2]. Several leading journals have also discussed how to increase the quality and outcome of CPR and the postcardiac arrest care (including strategic application of ECPR and hypothermia in treating pediatric or trauma patients). Applications of resuscitative endovascular balloon occlusion of the aorta (REBOA) for abdomen-pelvic hemorrhage and emergency vascular access for extracorporeal membrane oxygenation (ECMO) are also popular and timely [3–6]. In this special issue, we aim to focus on the field of emergency and critical care, particularly with a focus on the resuscitation of patients with a cardiac arrest and the care of patients during and after a cardiac arrest.

First, topics related to the use of videolight and conventional intubating stylet systems for emergency intubation were described in detail, and they were compared with other modes of intubation in COVID-19 setups. M-Y Wu et al. mentioned that digital devices can shorten intubation times, improve patient outcomes, and decrease the risk of infections among clinical staff, especially during the ongoing COVID-19 pandemic. In addition, M-F Wang et al. evaluated the CPR effectiveness that adolescents (12 years old) and adults could perform, and these are individuals who underwent the same courses for basic life support (BLS) and automated external defibrillators (AEDs). They found that the sixth-grade elementary students' performances in CPR and AED were similar to those of adults after completing the current 90-minute course. Therefore, they strongly advocated offering CPR and AED courses to 12-year-old children, and these courses should emphasize the importance of checking the breathing status of the patient.

The time and the process of transportation were key factors associated with patient outcomes. Puslecki et al.

analyzed the safety of ECMO support during medical transportation, and this was a single-center study and literature review. They reviewed 2,647 ECMO transfers, most of which were transported by ground transportation (91.6%). The rate of adverse events ranged from 1% through 20%. Only 4 deaths occurred during transport (mortality 0.15%). Moreover, L-H Huang et al. evaluated the threshold of the ambulance response time for predicting the survival to hospital discharge for patients with an OHCA. After analyzing 6,742 adult OHCA cases, they found that the adjusted OR of the EMS response time for the survival to hospital discharge was 1.217 (for each minute shorter, CI: 1.140–1299) and 1.992 (<6.2 min, 95% CI: 1.496–2.653). In the case of an OHCA in public areas or with bystander CPR administration, the threshold was prolonged, and when medical personnel performed CPR, the optimal response time threshold was shortened.

Zalewski et al. designed a randomized simulation cross-study and assessed the impact of the defibrillation methods on the CPR quality. They concluded that the simulation-based analysis revealed that the use of adhesive electrodes during defibrillation instead of standard hard paddles may improve the quality of the CPR performed by a two-person emergency team. In addition, M-S Hsieh et al. focused on sepsis and the following outcomes. They reported the risks of gastrointestinal bleeding (GIB) and major adverse cardiovascular events (MACEs) in 220,082 sepsis patients. Both GIB and MACEs significantly increased the risk of ICU admission and the risk of patients receiving mechanical ventilation but did not increase the risk of hospital mortality, which was independently associated with both acute myocardial infarction (AMI) and intracranial hemorrhage (ICH). C-J Li et al. performed a multicenter retrospective cohort study analyzing the treatment effect of dopamine and norepinephrine on hypotension among OHCA patients who achieved return of spontaneous circulation (ROSC). They concluded that there were no significant differences in the 30-day survival and that there were favorable neurologic performance rates between the post-ROSC hypotension treatment groups (between patients who received dopamine and those who received norepinephrine).

Finally, this special issue highlights several articles that report improvements in the CPR training, quality control, resuscitation strategies, and sepsis outcomes. We believe that readers will obtain useful information from this article.

Conflicts of Interest

The editors declare that they have no conflicts of interest regarding the publication of this special issue.

Yan-Ren Lin
Jacek Smereka
Kee-Chong Ng
John M. Ryan

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Research Article

Role of Trachway versus Conventional Modes of Intubation in Difficult Airway Management in COVID-19 Setups

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Difficult airway management in critically ill patients remains a difficult task associated with high morbidity and mortality rates. In difficult airway populations, prompt effective intubation is more important to prevent hypoxia and neurological injury. During the ongoing COVID-19 pandemic, prolonged intubation time and repeated intubation can lead to an increase in the risk of infection. Therefore, digital devices can shorten intubation times and decrease the risk of infection among clinical staff. The advantages of the Trachway videolight intubating stylet suit these conditions. Trachway stylet intubation is an effective method for video laryngoscopy to enhance patient safety and improve the intubation success rate. However, a few studies have focused on the effect of stylet intubation by reducing repeated intubation and oxygen desaturation. In this study, we reviewed current data of Trachway intubation and shared our four major training scenarios in Taipei Tzu Chi Hospital via the Trachway videolight intubating stylet system for emergency intubation, comparing them with other modes of intubation.

1. Introduction

During this critical era of the ongoing COVID-19 pandemic, airway intubation faces a challenge for high risk of COVID-19 infection, increased number of infected patients, straining health-care systems, and crashing local economies. Several types of video laryngoscopy have been reported to shorten intubation times and decrease the risk of infection among clinical staff [1–3]. The Trachway videolight intubating stylet system (Biotronic Instrument Enterprise Ltd., Tai-Chung, Taiwan) is a J-shape stylet fabricated using stainless steel, which is promoted for tracheal intubation because it easily passes through the oral cavity. The Trachway consists of three parts: a video recorder at the end of the stylet, grip, and screen. The video stylet can allow physicians to visualize the vocal cords and endotracheal tube passage. In general intubation, the patient is placed in a sniffing position for conventional direct laryngoscope intubation. However, direct laryngoscope intubation is difficult under several conditions (cervical spinal cord injuries, facial injury, and temporomandibular joint rigidity). The advantage of the Trachway videolight intubating stylet suits these conditions and provides effective intubation, compared to direct laryngoscopy. In addition, the Trachway videolight intubating stylet can also be transformed to video laryngoscopy by changing the J-shape stylet to the laryngoscope blade. Thus, one system is made to have two effective intubation methods. The transformation from Trachway video laryngoscopy to Trachway video intubating stylet is easy and quick. In this ongoing pandemic, the Trachway may significantly decrease the risk of COVID-19 infection by improving the preparedness of frontline doctors during emergency intubation, especially in emergency medical students, residents, and fellows. In this study, we reviewed

current data of Trachway intubation and shared our data in Taipei Tzu Chi Hospital. We equally used the Trachway videolight intubating stylet system to create four major scenarios for emergency intubation in COVID-19 patients, comparing them with other modes of intubation.

2. Methods

Our training program was held from August 2019 to June 2020. It included four training courses (Table 1). The manikin was placed on a standard stretcher, and our program was carried out in the emergency department. The four training courses were carried out on Laerdal Airway Management Trainer™ (Laerdal Medical Ltd, Orpington, UK) for medical students, residents, and fellows. In difficult airway management, the manikin was set up with an enlarged manikin tongue to create an upper airway obstruction. The four training courses included direct laryngoscopy, video laryngoscopy, Trachway stylet, and surgical airway. Before the four scenarios, all trainees participated in two-hour training lectures. After training lectures, the scenarios were performed immediately. In each scenario, we requested all trainees to perform endotracheal intubation thrice. In the first scenario, we compared the efficacy of the Trachway stylet to direct laryngoscopy and video laryngoscopy for intubation in normal adults. In the second scenario, we compared the Trachway stylet to direct laryngoscopy, video laryngoscopy, and surgical airway for difficult airway management. In the third scenario, we used the Trachway stylet for nasal intubation in a difficult airway. In the fourth scenario, we simulated the intubation in COVID-19 patients by direct laryngoscopy and video laryngoscopy in protective cover (Table 1).

3. Result

3.1. Trachway System in Orotracheal Intubation. The Trachway intubating stylet for digital intubation was induced by Ong et al. [4] in 2009, and they reported that the duration of intubation is approximately 21–25 seconds in manikins, which is adequate for clinical use. The Trachway intubating stylet provided an alternative tool for intubation. The Trachway intubating stylet is an intubating stylet just like a lightwand but with a camera for direct observation (Figure 1). During intubation, the Trachway stylet is inserted along the midline of the tongue to view the glottis. After the stylet passed through the glottis, the vocal cords would come into view, and then, the endotracheal tube is slid into the trachea. Using Trachway stylet intubation may not need to change head or neck position to facilitate intubation, and in a population with limited mouth opening, it may provide more easy intubation.

3.2. Trachway System in Nasotracheal Intubation for Difficult Airway. In recent years, the efficacy of the Trachway stylet system in nasotracheal intubation has been investigated. Hsu et al. [5] reported that 100 patients for oromaxillofacial surgery received nasotracheal intubation (NCT01917409) in comparison with the Macintosh laryngoscope and Trachway stylet assistance. In the Trachway stylet group, the total intubation time and duration of using tools to advancing the tube into the trachea were significantly shorter, compared to the laryngoscope group. The median score of the modified nasotracheal intubation difficulty scale was higher in the laryngoscope group. During intubation, up to 38% of patients needed cuff inflation and 54% patients needed BURP maneuver in the laryngoscope group, but no patients needed assistance in the Trachway group. The mean total intubation time in the Macintosh laryngoscope is about 2 min for trainees and 1 min for experienced intubators with Magill forceps, and the Trachway stylet nasointubation has a shorter mean total intubation time, 32.3 sec [6, 7]. Our study then provides supportive evidence for Trachway stylet nasointubation in difficult airway management, especially in patients with limited mouth opening. In our third scenario, we used the Trachway stylet for nasal intubation in a difficult airway (Figure 2). First, secretions of the oropharynx or hypopharynx may impede the view of the trachea. Suction with the DuCanto catheter, at least using Yankauer, may improve the view. Second, slowly inserting the tip of the endotracheal tube with the Trachway stylet from the selected nostril by the left hand is important to prevent epistaxis, which may cause poor visualization of the pharynx. The tip of the Trachway stylet is recommended to hind the inner tip of the endotracheal tube to prevent blurring. Finally, the Trachway is often held in the right hand, and the left hand can assist the insertion of the tip of the endotracheal tube through the left nostril. After the tip of the endotracheal tube passes through the nostril, it rotates 90° and elevates while crossing the midline as it fits the anatomy curve of the nasopharynx and oropharynx (Figure 3). In view of the laryngopharynx, the tip of the endotracheal tube was advanced to the target depth in a routine manner.

3.3. Trachway System in COVID-19 Intubation. In the fourth scenario, we simulated the intubation in COVID-19 patients. The trainers were intubated in an acrylic protective cover designed by Dr. Lai Hsien-yung (available at https://sites.google.com/view/aerosolbox/home) to decrease the risk of contamination [8]. This device consists of an acrylic box with an opening side to receive the patient's head and neck and two small holes for the intubator's hands on the opposite side. The monitor of the Trachway can be disconnected to the stylet and placed out of the box to prevent risk of contamination. A Trachway with a stylet or video laryngoscope was more effective for intubation (Figure 4). In the acrylic box, direct laryngoscopy is more difficult for intubation due to limitations of hand motion and visualization in small spaces. Video laryngoscopy is more suitable for the modified acrylic protective cover. To prevent risk of contamination, the Trachway system could wirelessly connect with the monitor. In addition, this system can connect with more than one monitor at the same time, thereby providing an effective teaching tool for medical students.

In this study, we also searched the PubMed databases for articles published from inception to October 2020. No limits were applied to our Boolean search strategy using the

Table 1: Four scenarios of the training program and simulation setting.

Scenarios	Classification	Devices
Scenario 1	Normal intubation	Trachway stylet vs. direct/video laryngoscopy
Scenario 2	Difficult intubation	Trachway stylet vs. direct/video laryngoscopy and surgical airway
Scenario 3	Difficult intubation (nasal intubation)	Trachway stylet
Scenario 4	COVID-19 intubation in protective cover	Direct laryngoscopy vs. video laryngoscopy

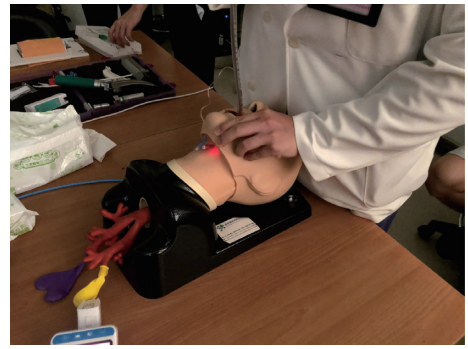

Figure 1: The tip of the Trachway intubating stylet is also equipped with the light, just like a lightwand, for guiding into the trachea by transillumination of the neck tissues.

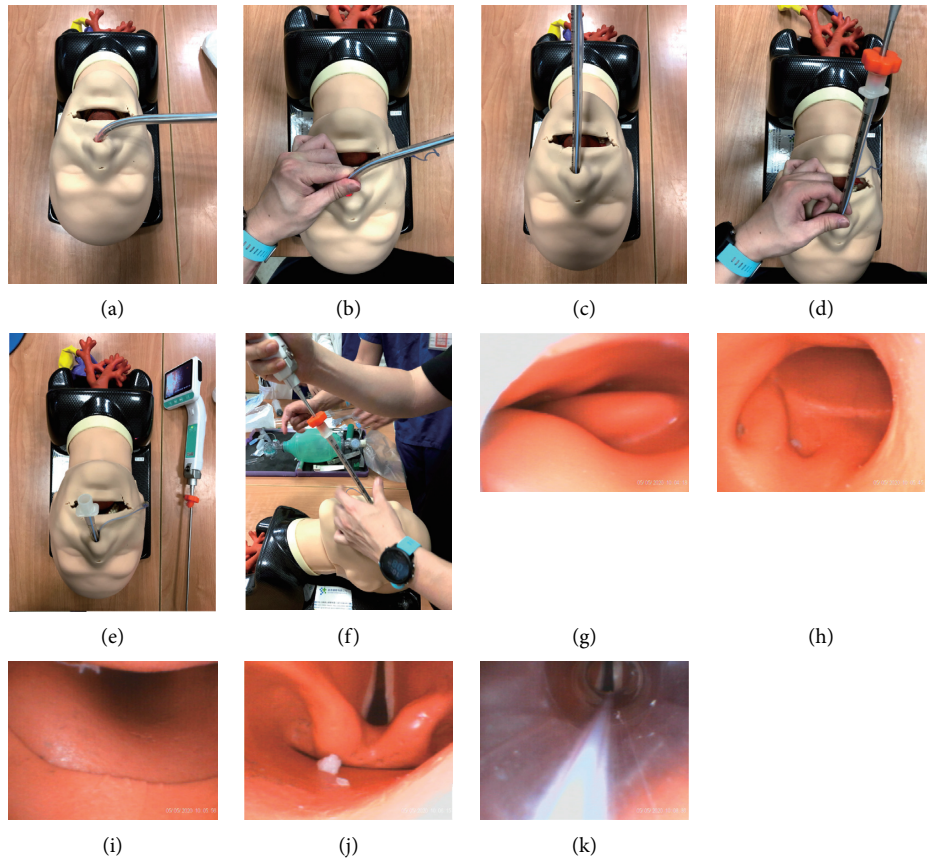

Figure 2: Using a Trachway stylet for nasointubation. (a) Inserting the tip of the endotracheal tube with a Trachway stylet from the selected nostril, (b) using the left hand to control the force and prevent from epistaxis, (c) 90-degree rotation and elevation of the Trachway stylet at the same time to midline, (d) making the curve of the Trachway stylet fit the anatomy curve of the nasopharynx and oropharynx, (e, f) the tip of the endotracheal tube was advanced to the target depth in a routine manner, (g, h) the view of inserting the tip of the endotracheal tube with the Trachway stylet in the nasopharynx, (i) the view of the tip of the endotracheal tube in the oropharynx, (j) the view of the tip in the laryngopharynx, and (k) the view of the tip of the endotracheal tube passing through the vocal cord.

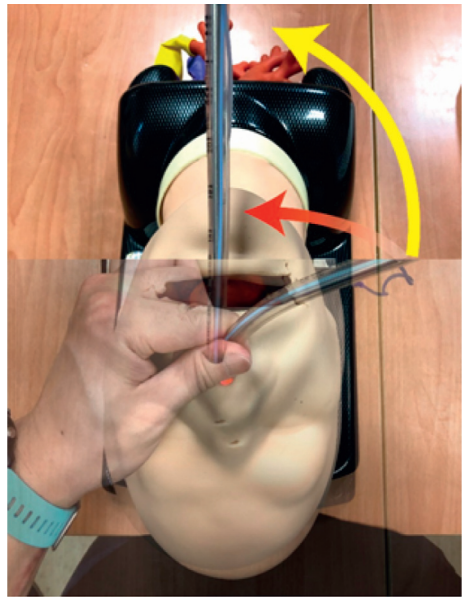

Figure 3: After the tip of the endotracheal tube is inserted into the selected nostril, 90-degree rotation (red arrow) and elevation (yellow arrow) of the Trachway stylet at the same time to midline make the curve to fit the anatomy curve of the nasopharynx and oropharynx.

(a) (b) (c)

Figure 4: (a) Trachway with a stylet or video laryngoscope is more effective to prevent contamination wirelessly. (b, c) Trachway system intubation is suitable to different acrylic protective covers.

keywords in bracket ("Trachway," "Trachway intubation," "difficult airway," "video laryngoscopes," and "intubation"). References from retrieved articles were also examined to identify other relevant articles. Studies were included if they used Trachway intubation systems. Studies were excluded if they were irrelevant to the study's aim or were animal studies. In total, 23 articles were included in the discussion analysis.

4. Discussion

Airway management in critically ill patients, suspected to be infected with COVID-19, by emergency physicians is a challenge, especially in difficult airways. In the current concept, shortening the intubation time and indirect intubation would decrease the risk of contamination. The role of video laryngoscopy and digital video stylet has become increasingly important for orotracheal intubation in high-risk patients [1–3]. Trachway stylet intubation is friendly for inexperienced physicians, and the effect of Trachway stylet intubation is similar to that of other video laryngoscopes. In Tseng et al.'s [9] manikin study, 36 medical students without previous experience in tracheal intubation were included to compare the Trachway intubation stylet and airway scope video laryngoscope. Overall success rates did not differ significantly between Trachway stylet intubation and video laryngoscopy. In intubation time, there was no significant difference as well. Kim et al. [10] found that the success rate for tracheal intubation is similar, but stylet intubation provided faster and easier intubations than the airway scope video laryngoscope. On comparing the Trachway intubating stylet and Macintosh direct laryngoscopy in a manikin study with 38 nurse anesthesiologists, it was revealed that the Trachway intubating stylet had shorter intubation times and proved easier with intubations than direct laryngoscopy in difficult airway management, but no difference was observed in the normal airway. In addition, the Trachway intubating stylet did not have any complication event as the direct

laryngoscope [11]. In Cooney et al.'s [12] study, attending and resident emergency physicians were included for intubation of a difficult airway in high-fidelity simulated patients with stylet intubation in comparison with direct laryngoscopy. The results showed a 100% first attempt success rate and a lower cumulative attempt time in the stylet intubation group. In current data, a Trachway with Macintosh laryngoscopy for intubation is recommended for medical learners. However, in experienced intubators (residents and fellows), the learning curve of Trachway stylet intubation is shorter. Hence, Trachway stylet intubation is a more effective, faster, and easier method, especially for difficult airway management.

In difficult airway management, awake intubation is a good choice but requires a skilled operator to perform it. Many video intubation devices provide an alternative method for physicians to awake tracheal intubation. The Trachway video stylet has a similar size but more rigidity compared to fibers. During Trachway awake intubation, the traditional transtracheal block, spray-as-you-go technique, is not attempted because of the lack of a working channel in this device. A novel modified method for Trachway awake intubation is needed [13]. The Trachway stylet and a 6 Fr suction tube were inserted into the lumina of a size 7 or larger endotracheal tube through the side-arm orifice of the double-swivel connector. After administration of lidocaine injection into the trachea from inner suction tube, an endotracheal tube was further advanced into the trachea. The Trachway stylet and suction tube were removed without the endotracheal tube. Poor visualization is a major problem in Trachway awake intubation. Oral secretions during the intubation process may cause poor visualization even after oral secretion. In obese or limited mouth opening population, excess airway tissue also leads to this problem. A jaw thrust or head-tilt maneuver may improve visualization during intubation. Poor visualization may prolong duration of intubation and increase discomfort to the conscious patient, especially in obese patients. In facilitating tracheal intubation, the Trachway is reported effective in anesthetized patients with difficult airway. In Hung et al.'s [13] report, we found that Trachway video stylet awake intubation is an alternative tool for difficult airway, especially in an emergency condition [14].

The efficacy of the Trachway stylet system for emergency nasotracheal intubation has been investigated. In a study by Lee et al. [15], 80 patients with limited mouth opening undergoing oromaxillofacial surgery were included and the results showed the mean total intubation time was significantly shorter in the Trachway group. In the modified nasal intubation difficulty scale analysis, only 55% of patients in the fiberoptic intubation group were categorized as having no difficulty with intubation unlike 100% of patients in the Trachway group. There were no significant differences in complication rates (bleeding from the nostril, accumulation of blood in the oropharyngeal space, postoperative sore throat, hoarseness, and pain on swallowing) between the two groups. Trachway stylet nasotracheal intubation provided shorter intubation time, better intubation conditions, and similar complication rates, compared with fiberoptic intubation. The Trachway stylet-assisted nasotracheal intubation was prevented from blind advancement by direct visualization of the path through the nasal cavity. The distal tip of the Trachway stylet can be positioned in the nasotracheal tube to prevent damage to the nasal tissues. Therefore, using the Trachway stylet for nasointubation is an alternative tool for difficult airway management and a rescue method for emergency conditions [16].

5. Conclusions

In this study, we shared with our experience and concluded from previous reported studies that the Trachway stylet intubation system provided more effective, faster, and higher success rates of intubation than direct laryngoscopy. In addition, the advantages of the Trachway system included wireless connection, reducing the risk of contamination during airway management in COVID-19 patients.

Data Availability

No data were used to support this study.

Conflicts of Interest

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

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Research Article

Learning Effectiveness Assessment between Primary School Students and Adults in Basic Life Support Education

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Background. Out-of-hospital cardiac arrest (OHCA) remains a big issue of critical care. It is well known that bystander cardiopulmonary resuscitation (CPR) with an automated external defibrillator (AED) used did improve the survival rate. Therefore, CPR education including basic life support (BLS) and AED has been advocated for years. It showed significant improvement of knowledge and willingness to perform CPR through adolescents after the course. However, little is known regarding the ability and learning effectiveness of school students who attend such courses. Therefore, this study aimed to evaluate the CPR effectiveness of both adolescents (12 years old) and adults who undergo the same course of BLS and AED. *Methods*. This is a retrospective study. Sixth-grade elementary school students in Northern Taiwan were selected to compare with the adult group. Both took 90 minutes of the BLS and AED course by the doctor with BLS instructor qualification. The primary outcomes were CPR quality and passing or failing the skill examination parameters. The secondary outcome was the posttraining written test and questionnaire of CPR willingness. *Results*. In the written test, there was a statistical difference in the pretest score except AED knowledge, but no difference was revealed in the posttest score. No statistical difference in CPR quality was noted. In the skill examination, only checking breathing status had statistical difference (elementary group (71%) vs. adult group (86%) ($p = 0.003$)). *Conclusion*. We revealed that sixth-grade elementary students' performance in CPR and AED was similar to that of adults after completing the current 90-minute course. Therefore, we strongly advocate offering CPR and AED courses to 12-year-old children, and these courses should emphasize checking the victim's breathing status.

1. Introduction

Out-of-hospital cardiac arrest (OHCA) is a critical public health concern. OHCA has a lower incidence rate compared with other diseases; however, it has a high mortality rate. In the United States, the OHCA rate per 100,000 people is 3.5 [1]. Between 2000 and 2012 in Taiwan, approximately 51.1 people per 100,000 experienced OHCA [2]. According to a study conducted in Paris, up to 70% of OHCAs occur in residential areas, and 30% occur in public areas [3]. Moreover, a recent retrospective study in Taiwan with data from 2012 to 2016 revealed that 80% of OHCAs occur in private places [4]. A systematic review also reported that approximately 53% of events are witnessed by a bystander, and bystander cardiopulmonary resuscitation (CPR) remains low at 32% [5]. However, bystander CPR rates vary

considerably worldwide, ranging from 10% to 65% in the United States [6]. Multiple factors are responsible for these large differences in the bystander CPR rate, including social economic status, racial and educational characteristics, and location of the collapse [7–9].

Bystander CPR with an automated external defibrillator (AED) is widely known to improve the survival rate. Moreover, bystander CPR significantly increases (by up to two- to four-fold) 30-day and 1-year survival regardless of witnessed status [10]. Nevertheless, according to related studies in Taiwan, bystander CPR rates before the arrival of an emergency medical technician (EMT) ranged from 17% in 2008 to approximately 30% between 2012 and 2016 [4, 11]. According to a US study, bystander CPR rates have increased slightly over time: from 28.2% in 2005-2006 to 36.3% in 2012 [12]. CPR education has been expanding for years, with considerable public health benefits; however, obstacles remain regarding the execution of CPR by the public. According to a study conducted in Taiwan, the main reasons people hesitate to perform CPR are fear of legal consequences (44%) and harming patients (36.5%) [13]. Concerning the legal aspect, the Good Samaritan Law was passed in 2013 in Taiwan to protect people against legal consequences if they perform CPR incorrectly on a stranger in a critical situation. In addition to legal protection, CPR educational training should also be promoted to increase people's willingness to perform CPR.

Currently, the American Heart Association (AHA) has a specific education program for adolescents. In Taiwan, CPR education has been provided for high-school students for years. To extend the benefits of such training, we started a new CPR training program in Taiwan for adults, and it revealed noninferior results to the conventional CPR training program [14]. However, little is known regarding the ability and learning effectiveness of school students who attend such basic life support (BLS) and AED courses. A European group named Kids Save Lives has claimed that training school children in CPR is highly effective, and 12 years is the suitable age to start teaching cardiac compression [15]. However, CPR quality is highly related to the body mass index (BMI) and exercise habits in EMTs [16]. Whether current adult CPR teaching programs are suitable for adolescents and whether these younger students can achieve the same CPR effectiveness as adults remain unknown. Therefore, the purpose of this study was (1) to evaluate the CPR effectiveness of both adolescents (12 years old) and adults who undergo the same course related to BLS and AED in the same environment and (2) to prove that the current adult BLS course is suitable for adolescents.

2. Method

2.1. Study Design, Setting, and Participants. This retrospective observation study was approved by the Chang Gung Memorial Foundation Institutional Review Board (approval number: 202000464B0). We extracted data from the database of an education program (IGOGO) and considered training courses between January 2018 and July 2018. The extracted data had to meet inclusion criteria, including students having the same training date and classroom, and participants were subsequently divided into an elementary sixth-grade students (elementary group) and adult group. The purpose of the training program was to promote the long-term implementation of CPR teaching combined with the use of AED for the public. To evaluate learning effectiveness in both elementary school students and adults, we selected participants who did not receive any CPR training for at least 1 year prior to taking this training course. Participants who were unable to kneel to perform CPR and those who were pregnant were excluded. A total of 308 participants were analyzed in the study, including sixth-grade students and teaching staff, security guards, and volunteers.

2.2. Education Course. IGOGO in Taiwan has been offering courses for many years. We use a standard 90-minute BLS training program, which is similar to the AHA course. The AHA program is a 90-minute, instructor-led, and classroom-based training program that employs the practice-while-learning format. The learning content includes an introduction to relevant laws, the purpose of CPR and AED, chains of survival, demonstration of the adult BLS sequence, CPR with AED use, and hands-on compression-only adult CPR.

The IGOGO program is taught by emergency physicians with BLS instructor qualifications who are assisted by nurses and doctors. The ratio of participants to manikins to instructor is 8 : 4 : 1. Sensor-equipped manikins (Resusci Anne with QCPR, Laerdal Medical AS, Norway) were used in the 2-minute hands-on practice in both groups. Each course consisted of a 60-minute CPR teaching video with practice, 20 minutes of instruction related to AED operation, and a 10-minute discussion concerning the legal aspect of bystander CPR in Taiwan.

2.3. Data Collection. Data collection focused on training program-specific data and the demographic data of participants. We also obtained informed consent from all participants and removed any personally identifiable information. We compiled course-related information, including basic student and adult data (which contain age, weight, height, gender, previous exercise habits, whether there is any previous CPR learning experience, and when was the last learning experience), pretest and posttest (e.g., knowledge of CPR and AED) results, skill tests, and CPR willingness questionnaire, into a database [17] (Appendix 1 in Supplementary Materials). All questions in the written test were formulated by staff of the Taiwan Society of Emergency Medicine, Emergency Medical Services Department. We assessed learning effectiveness in several manners. We assessed CPR and related knowledge by using a written test, which contained 15 multiple-choice questions with a maximum score of 100 (Appendix 2 in Supplementary Materials). CPR performance was evaluated in two aspects: manikin feedback and examiner evaluation. Objective data, including compression depth, compression rate, and full chest recoil, were recorded and collected from the

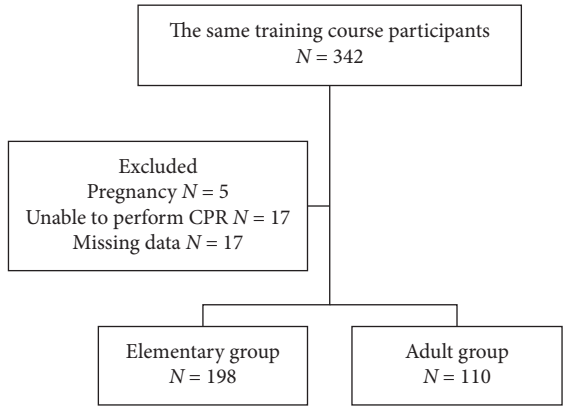


Figure 1: Flowchart. *N*: number; CPR: cardiopulmonary resuscitation.

feedback manikin. We followed the updated 2015 AHA Guidelines for CPR and Emergency Cardiovascular Care, in which high-quality CPR is defined as follows: (1) a compression rate of 100–120 beats per minute (bpm), (2) a compression depth of 5–6 cm, and (3) full chest wall recoil. Examiners rated participants' performance individually. Examiners assessed how well participants followed the BLS sequence in terms of skills on the checklist—from verifying scene safety to AED use (Appendix 3 in Supplementary Materials). We count each pass step as one point and fail step as zero points (total scores are 8). Ventilation was not included in this educational program because compression-only CPR is the current recommendation.

2.4. Outcome Measures. The purpose of this study was to compare CPR effectiveness between elementary students and adults in the same setting (i.e., learning subject and environment). The primary outcomes were CPR quality (a compression rate of 100–120 bpm, a compression depth of 5–6 cm, and full chest wall recoil) and passing or failing the following skill examination parameters: (1) confirm safety, (2) check consciousness, (3) call for help, (4) check breathing status, (5) CPR location, (6) CPR posture, (7) AED operation, and (8) AED pad location. The secondary outcome was the posttraining written test, questionnaire of CPR willingness, and total scores of skill examination (Appendices 1 and 2 in Supplementary Materials).

2.5. Statistical Analysis. Categorical variables were compared using the chi-squared test and are presented as numbers and percentages. Continuous variables are presented as means and standard deviations, and Student's *t*-test was used to compare the difference between two groups. The significance level α was set at 0.05. The data were analyzed using IBM SPSS Statistics (version 25.0 for Windows; IBM Corp., Armonk, NY, USA).

3. Results

In total, 342 people participated in the training program including 210 students and 132 school staff (Figure 1). We excluded those who were pregnant, were unable to adequately perform CPR, or had incomplete information; thus, 308 participants were eligible for analysis. Among them, 198 were elementary school students and 110 were school staff. Table 1 lists the demographic statistics of the study. The mean age of elementary students was 11.8 years, and that of adults was 37.3 years. Females accounted for approximately half of the elementary group and 69% of the school staff. The two groups differed in terms of BMI, sport habits, and CPR learning experience.

The elementary group and adult group scored no difference in posttest (elementary group = 89.77; adult group = 91.62; $p = 0.064$; Table 2). Regarding CPR quality, the elementary group achieved, on average, 114 bpm, a full chest recoil rate of 75.7%, and a compression depth of 4.68 cm. The adult group achieved, on average, 113 bpm, a full chest recoil rate of 77.2%, and a compression depth of 5.22 cm. In terms of CPR quality parameters, no significant

Table 1: Demographic population.

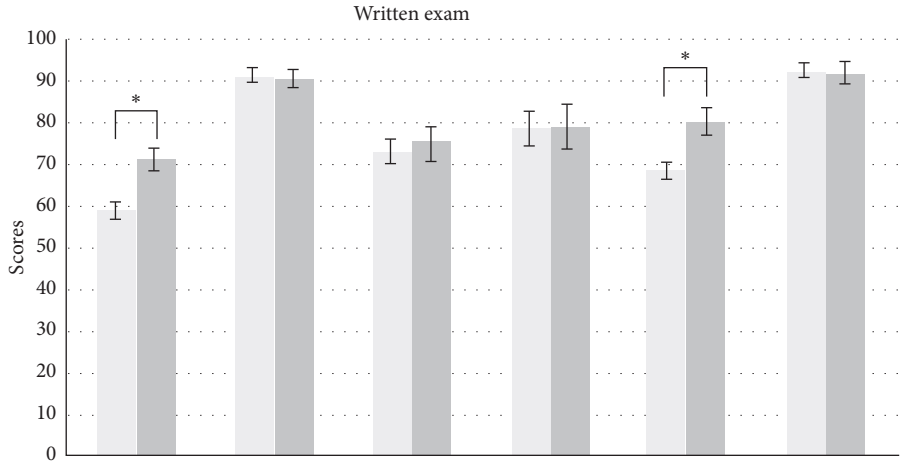
	Elementary group	Adult group
Numbers	198	110
Age, years (SD)	11.8 (0.46)	37.27 (10.22)
Height, cm (SD)	152.8 (7.32)	160.77 (7.36)
Weight, kg (SD)	41.9 (8.70)	60.75 (11.43)
BMI (SD)	17.83 (3.018)	23.85 (3.357)
Female (%)	101 (51.01%)	76 (69.09%)
Sport habits (%)	154 (77.78%)	51 (46.36%)
<1 hour	122 (61.62%)	28 (25.45%)
>1 hour	32 (16.16%)	23 (20.91%)
CPR learning experience (%)	64 (32.32%)	94 (85.45%)
1~2 years	48 (24.24%)	72 (65.45%)
>2 years	7 (3.54%)	10 (9.09%)
Unknown	9 (4.54%)	12 (10.91%)
Type of CPR (%)		
Hands-only CPR	55 (27.78%)	71 (64.54%)

Data are expressed as mean (SD) or *n* (%). cm: centimeter; kg: kilogram; SD: standard deviation; BMI: body mass index; CPR: cardiopulmonary resuscitation.

Table 2: Assessment of the cardiopulmonary resuscitation training course.

	Elementary group	Adult group	*p* value
Post-written test score (SD)	89.77 (8.28)	91.62 (8.68)	0.064
CPR (SD)	91.75 (12.00)	90.78 (12.33)	0.499
AED (SD)	78.92 (26.67)	79.09 (27.78)	0.872
Others (SD)	92.61 (11.66)	92.18 (13.57)	0.77
Quality assessment			
BPM (SD)	114.15 (20.556)	113.17 (13.03)	0.18
Recoil (SD)	75.7 (32.0)	77.2 (31.0)	0.33
Depth (SD)	4.68 (0.95)	5.22 (0.81)	0.12

Data are expressed as mean (SD). SD: standard deviation; CPR: cardiopulmonary resuscitation; AED: automated external defibrillator; BPM: beats per minute.



	CPR		AED		Others	
	Before	After	Before	After	Before	After
Elementary group	59.18	91.75	73.22	78.92	68.52	92.61
Adult group	71.22	90.78	75.09	79.09	80.45	92.18

Figure 2: Difference of pre-/post-written exam after training. Data are expressed as score. * indicates a significant difference. CPR: cardiopulmonary resuscitation; AED: automated external defibrillator.

Table 3: Skill examination parameters of cardiopulmonary resuscitation.

	Elementary group	Adult group	p value
Numbers	198	110	
Confirm safety	123 (62.12%)	72 (65.07%)	0.561
Check consciousness	172 (86.87%)	92 (83.64%)	0.437
Call for help	163 (82.32%)	94 (85.45%)	0.479
Check breathing status	142 (71.72%)	95 (86.36%)	0.003*
CPR location	154 (77.78%)	91 (82.73%)	0.302
CPR posture	153 (77.27%)	92 (83.64%)	0.185
AED operation	160 (80.81%)	95 (86.36%)	0.216
AED pad location	156 (78.79%)	96 (87.27%)	0.064
Total scores	6.18 (1.284)	6.61 (1.342)	0.006*

Data are expressed as mean (SD) or n (%). * indicates a significant difference. SD: standard deviation; CPR: cardiopulmonary resuscitation; AED: automated external defibrillator.

differences were observed between the two groups (Table 2). Figure 2 reveals a considerable improvement in both groups after taking the 90-minute course. The elementary and adult groups differed significantly in the pretest, except for AED knowledge. However, it showed no statistical difference in all three items (CPR, AED, and others) after the course.

Regarding skill items shown in Table 3, elementary students performed CPR as effectively as adults in almost all skills including verifying scene safety, checking consciousness, calling for help, CPR location, CPR posture, AED operation, and AED pad location. However, a significant difference was observed in checking breathing status and total scores: the success rate in the elementary group was 71%, whereas it was 86% in the adult group ($p = 0.003$), and total scores were 6.18 (1.284) and 6.61 (1.342), respectively. We also investigated willingness to perform CPR. The results revealed no difference in willingness to perform hands-only CPR on an acquaintance but a significant difference in willingness to do so on a stranger (elementary group = 51%; adult group = 39.1%; $p = 0.045$; Table 4). The three major reasons why participants were unwilling to perform CPR on either an acquaintance or a stranger are fearing doing further harm, fearing performing CPR incorrectly, and being unwilling to perform cardiac compression.

4. Discussion

Our results revealed that, after undergoing the same training program, sixth-grade elementary students could perform CPR as effectively as adults could in three aspects, namely, compression depth, compression rate, and full chest recoil. However, elementary students struggled to meet the AHA high-quality benchmark for compression depth. In a study of school children aged 7–14 years, chest compression depth was highly correlated with children's age, weight, height, and BMI [18]. In a UK study that divided children into three groups, namely, 9-10, 11-12, and 13-14 years, only the 13-14-year-old group could perform chest compression just as well as adults [19]. Therefore, when teaching high-performance CPR to elementary school students, instructors should focus on the knowledge and process, instead of requiring students to reach the depth mentioned in the AHA guidelines because of the children's limited ability to perform chest compression. Notably, the children and adults differed significantly in terms of checking breathing status despite following the same learning program and checklist; previous similar studies have not noted this disparity. Hence, instructors should devote special attention to teaching elementary students how to check breathing status in the future.

Currently, no regulations or rules stipulate when to implement CPR education in school settings in Taiwan. However, such programs are typically introduced in high school. According to the Kids Save Lives group in Europe, CPR training should start from the age of 12 years or even younger; moreover, annual CPR refresher courses should be

Table 4: Willingness to perform CPR after training.

	Elementary group	Adult group	p value
Willing to perform CPR on the associate			
Yes	188 (94.95%)	99 (90.0%)	0.099
No	10 (5.05%)	11 (10.0%)	
Reasons of unwillingness			
Afraid of doing further harm	10	5	
Afraid of doing CPR incorrectly	10	7	
Unwilling to perform cardiac compression	9	4	
Afraid of legal issues	7	11	
Others	4	2	
Willing to perform CPR on a stranger			
Yes	101 (51.01%)	43 (39.09%)	0.045*
No	97 (48.99%)	67 (60.91%)	
Reasons of unwillingness			
Afraid of doing further harm	43	37	
Afraid of doing CPR incorrectly	35	28	
Unwilling to perform cardiac compression	31	24	
Afraid of legal issues	27	8	
Others	23	21	

Data are expressed as n (%) or n. * indicates a significant difference. CPR: cardiopulmonary resuscitation.

offered [20–22]. Training can be offered successfully with a low-cost manikin and equipment by either medical professionals or educated teachers [23]. Studies have reported that children aged 10–12 years have the same CPR effectiveness as adults do [22, 24]. Our results corroborate those findings. In the written test, both children and adults exhibited considerable improvement between the pretest and posttest. Moreover, the 12-year-old elementary students had sufficient ability to undergo current CPR education and could comprehend and apply the training as well as adults could. Notably, AED knowledge in the pretest did not differ significantly between the two groups. This finding may be attributed to the widespread public-service announcements related to AED and also the implementation of AED in the school where our study was conducted. Therefore, as AED installations become more common, both promotion of AED and people's knowledge of it will increase.

Children included in this study could complete the CPR checklist items just as well as adults for almost all elements. However, children's performance in checking breathing status was inferior to that of adults; they either forget this element or performed it incorrectly. Checking breathing status is also a difficult task for adults: in conventional CPR education, adults struggle to differentiate bradypnea or agonal breathing. Thus, challenges faced by adolescents in CPR education might be understandable. A systematic review revealed that, by the age of 11-12 years, children can establish whether a victim is conscious and breathing normally [25]. We suggest to use virtual reality, augmented reality, and gamified learning to enhance the effectiveness of learning in the education program [26]. Results for AED pad location in the current study also merit further attention. Although the two groups did not differ significantly, the numerical difference was quite large (71.72% vs. 86.36%). Thus, children may easily confuse the correct placement of an AED. For CPR education to have the same effectiveness in both children and adults, we argue that such programs should focus more on checking breathing status and AED pad location. More crucially, children should be taught to activate the local emergency medical services system earlier because most cardiac arrest cases occur in residential areas [3, 4].

Whether children can perform CPR adequately still requires further study. In a study in a rural area of Taiwan, a 50-minute CPR/AED course significantly improved the knowledge of adolescents and empowered them to be willing to perform CPR if necessary [27]. Our study revealed the same trend. Children seem to be more willing to perform CPR on either a stranger or an acquaintance. Therefore, early promotion of CPR education is valuable for elementary school students. As a result of such training, the bystander CPR rate might increase in the future. In addition, in our questionnaire, children reported anxiety regarding performing CPR on strangers mostly because they fear causing harm if they perform it incorrectly; adults were more concerned with the legal aspect and contracting an infectious disease [28, 29]. Such reluctance may be overcome with sufficient training and by boosting children's confidence.

To sum up, we advocate offering the current 90-minute BLS and AED course to sixth-grade elementary students because they can understand the content and perform CPR as effectively as adults can. More widespread training may increase bystander CPR rates and subsequently result in survival benefits for those experiencing OHCA worldwide.

5. Limitation

This retrospective study was conducted with data from the IGOGO database; as a result, it has some limitations. First, we evaluated the performance in an educational setting; the current results may not represent children's actual performance when facing a real emergency situation. Finally, this

study did not track the learning status; hence, we could not assess whether children's CPR abilities are maintained over time; this aspect may be considered in future research.

6. Conclusion

In summary, we revealed that sixth-grade elementary students' performance in CPR and AED was similar to that of adults after completing the current 90-minute course. Because children are more willing to perform CPR than adults are, we strongly advocate offering CPR and AED courses to 12-year-old children, and these courses should emphasize checking the victim's breathing status.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request (e-mail: ngowl@ms3.hinet.net).

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Ming-Fang Wang and Yi-Kan Wu contributed equally to this work. Cheng-Yu Chien and Chip-Jin Ng contributed equally to this work.

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Supplementary Materials

CPR willingness questionnaire. (*Supplementary Materials*)

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Research Article

Patient Safety during ECMO Transportation: Single Center Experience and Literature Review

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Background. Extracorporeal membrane oxygenation (ECMO) has been proven to support in lifesaving rescue therapy. The best outcomes can be achieved in high-volume ECMO centers with dedicated emergency transport teams. *Aim*. The aim of this study was to analyze the safety of ECMO support during medical transfer on the basis of our experience developed on innovation cooperation and review of literature. *Methods*. A retrospective analysis of our experience of all ECMO-supported patients transferred from regional hospital of the referential ECMO center between 2015 and 2020 was carried out. Special attention was paid to transportation-related mortality and morbidity. Moreover, a systematic review of the Medline, Embase, Cochrane, and Google Scholar databases was performed. It included the original papers published before the end of 2019. *Results*. Twelve (5 women and 7 men) critically ill ECMO-supported patients with the median age of 33 years (2–63 years) were transferred to our ECMO center. In 92% ($n = 11$) of the cases venovenous and in 1 case, venoarterial supports were applied. The median transfer length was 45 km (5–200). There was no mortality during transfer and no serious adverse events occurred. Of note, the first ECMO-supported transfer had been proceeded by high-fidelity simulations. For our systematic review, 68 articles were found and 22 of them satisfied the search criteria. A total number of 2647 transfers were reported, mainly primary (90%) and as ground transportations (91.6%). A rate of adverse events ranged from 1% through 20% but notably only major complications were mentioned. The 4 deaths occurred during transport (mortality 0.15%). *Conclusions*. Our experiences and literature review showed that transportation for ECMO patients done by experienced staff was associated with low mortality rate but life-threatening adverse events might occur. Translational simulation is an excellent probing technique to improve transportation safety.

1. Introduction

The Extracorporeal Life Support Organization (ELSO, Ann Arbor, MI, USA, http://www.elso.org) is a worldwide nonprofit patronage organization of more than 900 centers units providing almost 200,000 ECMO per year [1]. The main mission of ELSO is to collect data on ECMO applications and develop guidelines regarding all aspects of therapy, including transport of EMCO-supported individuals [2].

ELSO recommends creation of centers dedicated to treat patients by means of sophisticated extracorporeal techniques, including ECMO. Due to its complexity, outcomes were shown to correlate with center volume. Therefore, the minimum number was set at the level of 6 applications per year [3–8]. The optimal number that has been linked to significant reduction in mortality is at least 30 adult supported individuals per year. As a consequence, consolidating of ECMO therapy in the specialized large-volume centers has been strongly recommended. Such centralization has introduced a highly specialized patient transport between referring hospitals and reference centers. This model has been adopted around the world and has been confirmed as save and associated with the optimal outcomes [3, 4, 9, 10].

The main aim of this study was to assess the safety of patients transported during the use of extracorporeal techniques on the basis of our experience as a referral hospital for ECMO-treated patients, a coordinating body in innovation and cooperation, as well as a systematic review of previously published clinical reports.

2. Methods

2.1. Analysis of Our Experience. We analyze the safety of ECMO patients transferred from the regional hospitals to our ECMO center in the last five years. To prepare for the first real life transport by conventional emergency ambulance, we performed simulation scenario that involved a case of refractory respiratory failure in one city approximately 80 km from referential ECMO center. It was blinded for physicians and paramedics engaged in on-site intervention, transportation, and admission to destination hospital. All weak points were found, analyzed, and discussed in detail and actions to improve safety have been developed.

2.2. Transfer of Patients. Analysis of transfer of our ECMO-supported patients, including patients' basic demographic variables, indications and modes of support (venovenous or venoarterial), and transportation characteristics, was performed. Special attention was paid to "in transportation" safety, including mortality and morbidity.

2.3. Data Management. As continuous variables such as age of studied patients and length of transfer have not satisfied criteria of normality (estimated by means of the Shapiro-Wilk test), they were presented as the medians with ranges (minimal through maximal values).

2.4. Systematic Review. A systematic review of the Medline, Embase, Cochrane, and Google Scholar databases was performed to find articles reporting primary or secondary ECMO transportation. Studies were included if they described medical or technical complications during interhospital transfers of patients with extracorporeal support. It included the original papers published before the end of 2019 and the search string was comprised of the following MeSH (Medical Subject Headings) and Booleans: (("Extracorporeal Membrane Oxygenation"[MeSH] OR "ECMO"[MeSH]) AND ("Transportation"[MeSH] OR "Patient Transfer"[MeSH])) AND "critical"[MeSH Terms] AND "adult"[MeSH Terms] and "safety"[MeSH Terms].

In addition, the following inclusion criteria including papers in English, published after 2009 in the form of randomized controlled trials (RCTs), meta-analyses, practice guidelines, and reviews were used. Articles dealing with the outcomes of exclusively pediatric and neonatological transfers, conventional transports without ECMO support, and the case studies were excluded. Three investigators reviewed all articles, performed data extraction, and compiled the database using equal digital templates (MP, KB, and MD). The search results were checked for the title and content of the abstract; then, the full text for review was obtained. Only the latest publications from a reporting center were included in the study. Results were compared, and discrepancies were solved by agreement. Duplicated results were obviously excluded. A fourth investigator approved the final database and decided upon remaining conflictive data (BP). In case of suspected unreliable information due to insufficient clarity in data presentation, a given article was excluded from the analysis or was solved by consensus of the research team. The process followed the PRISMA guidelines for systematic reviews and meta-analyses and the Cochrane guidelines for systematic review of interventions.

Once appropriate articles were allocated, the following general study and technical information were collected: center and country of realization, year of study start and year of its completion, reported period, number of transportation, primary/secondary transfer, vehicle type, deaths or adverse events, minimal and maximal transfer length, type of ECMO support (venovenous or venoarterial), and number of ECMO team persons. Patient deceases were considered to be attributable to complications during ECMO transportation whenever authors of the original article clearly identified a direct relation between the occurrence of the complication and the fatal outcome. Such complication must have occurred during the transfer and not related to cannulation.

A critical analysis of all aspects of transportation with ECMO support was made. In addition, attempts were made to identify the key components of this process that affects the patient's safety [11–32].

3. Results

3.1. Primary Simulation Scenario. This has previously been described in much detail in earlier authors' publication [32]. A video-film was recorded and carefully analyzed by all members involved in cooperation of mobile ECMO team.

The purpose of the created high-fidelity scenario was to verify the ECMO transportation procedure created for the "ECMO for Greater Poland" program. The simulation tested the communication and collaboration of several medical teams in prehospital and hospital settings. The specific objectives of the simulation were conducted to assess critical points and compiled into the scenario checklist for the ECMO transportation algorithm. That "probing simulation" creates transportation procedure for our dedicated mobile ECMO team to set standards for the future real-time/real-life ECMO transportation.

3.2. Our Experience. Twelve critically ill ECMO-supported patients (5 women and 7 men) with the median age of 33 (2 to 63) years were transferred to our ECMO center. 91% ($n = 11$) of our patients were in the venovenous (VV) mode with the remainder 8% being venoarterial (VA). The median transfer length was 45 km and ranged from 5 to nearly 200 km. In all cases, mobile ECMO team consisted of 4 of 5 members representing critical paramedics (1 or 2), perfusionist, cardiac surgeon, and specialist in intensive care. A number of professionals involved in transportation depended on ambulance type and in ECMO-dedicated vehicles there were was 5 persons whereas there were 4 in conventional ambulances.

The predominant indication for mobile ECMO team activation was deteriorating respiratory failure, refractory to conventional therapy with mechanical ventilation (11 cases). Preferable technique for cannulation was the percutaneous approach and only in one case surgical exposure of the peripheral vessels was carried out. One VA support and subsequent transportation were done when the patient was connected to intra-aortic balloon pump (IABP) that had been inserted a few hours earlier. In our group, nobody died and no adverse events were observed. The details are summarized in Table 1.

3.3. Literature Review. In total, 68 publications were found and at the very beginning of study selection 38 of them was excluded because they did not meet the established criteria (they included only pediatric or neonatological transports; their full text was not published in English or accepted as Letters to Editor). Thirty full text articles satisfied the search criteria; thus, they have been reviewed. Another 8 papers were discarded after detailed analysis due to type of reports (case studies) or because they did not include any ECMO transfer data (transfer type, transfer vehicles, distances, and adverse events). Eventually, 22 articles were analyzed, as shown in Figure 1.

A total number of 2647 transfers were reported. Among them, in 8 publications, more than 100 patient transportations were described. They were predominantly primary transfers (90%) and ground transportations (approximately 91.6%). Of note, various means of transport such as ambulance, helicopter, plane, or hybrid transfer (ambulance + helicopter, ambulance + plane, ambulance on the plane) were employed. The median number of reported transfers per month was 1.2. The median of minimal distance was 5 km (0.5–126) and the median of maximal one was 225 km (25–11398.2). Although all teams had been prepared to apply either VV or VA support, the vast majority of critically ill patients required VV support. The number of team members ranged from 2 to 6 people (median 3) (Table 2).

In the authors' analysis, only 15 deaths out of 2647 adult patient transfers were reported in the years 2013 to 2019 [12, 13, 23, 25, 28, 31]. In that group, there were 11 deaths associated with cannulation but not directly to transportation and only 4 (0.15%) were directly related to medical transfers to referential centers; see [12, 25, 31]. In the Bryner series published in 2014, 5 patients died (mortality rate 2.3%) before transport and one (0.5% mortality) died during preparations for takeoff of the fixed-wing aircraft [12]. Another death reported by Brechot et al. [25] was caused by significant hemodynamic deterioration during transport. Two last deaths were reported in Bromar et al. publication and in next report from Karolinska center by Fletcher-Sandersjoo et al. The mortality rate was 0.15% of transports of ECMO-supported patients.

Other described procedural complications did not affect survival. The adverse events rates have been found in the wide range from 1% to even up of 20% according to Fletcher-Sandersjoo et al.

Austin et al. reported technical problems in 7.3% transfers that included ECMO pump power failure ($n = 3$), ventilator ($n = 1$) or infusion pump failure ($n = 1$), and oxygen depletion ($n = 1$). Four patients required electrotherapy at the time of transfer (pacing = 3, cardioversion = 1). Tamponade of the pericardium and aeration of the system were noted twice. The original cannulation strategy was changed twice. The most common problems were hypothermia ($n = 8$), hypotension ($n = 11$), and hypoxia ($n = 17$) [26].

Sherren et al. described one case of recirculation (2.0%) and one case of death at the initiation of therapy in the reporting center (patient with multiple organ failure and history of multiple cardiac arrests). Additionally, hypoxia, hypotension, and arrhythmias classified as low-order adverse events were sporadically observed (only in 31% of transfers) [13].

Ehrenhaut et al. recorded death before departure ($n = 4$) and cardiac arrest before departure followed by return of spontaneous circulation ($n = 4$). Additionally, they reported 15.6% complications including incorrect position of the cannula ($n = 7$) and problems with identification of the peripheral vessel ($n = 7$). They also reported 6.3% high-risk complications such as hemodynamic instability ($n = 1$), bilateral tension pneumothorax ($n = 1$), and another problem with ventilation ($n = 1$). Two incidents occurred while driving [28].

Vaja et al. reported (1.0% complications) severe arrhythmias (ventricular tachycardia) during cannulation followed by return to spontaneous circulation [14].

Blecha et al. distinguished three sources of events related to total 431 transfers (52 on ECMO, 379 conventional without extracorporeal support):

Patient: this included cardiac arrest ($n = 3$), accidental extubation ($n = 2$), hypoxia ($n = 30$), and hypotension ($n = 7$)

Technical items: these included mainly problems with the respirator ($n = 3$)

Means of transport: this included a need to change the ambulance ($n = 3$) and unplanned delays (due to staff, weather, and others). No high-risk complication in ECMO support transfers was reported [22]

Guenther et al. listed the wrong position of the cannula ($n = 1$) and the failure of invasive blood pressure monitoring ($n = 1$) [19].

Heuer et al. noticed sudden reduction in the ECMO flow due to hypovolemia [24]; Salna et al. marked one incident of partial pressure changes associated with high attitudes [16] and 7.6% of patients in Brechot group manifested significant hemodynamic deterioration during transport [25]. The other authors did not report high-risk and life-threatening complications [11, 15, 17, 18, 20, 21, 23, 27, 29, 30, 32].

4. Discussion

4.1. Patients' Volume. In the ELSO guidelines recommending the development of ECMO centers, the rationale for strategy was reports showing the centers performing over 20–30 therapies per year that had clearly better outcomes. By creating ECMO centers according to the health needs of the population and accumulating both sufficient patients and experienced staff in these centers, the effectiveness of this challenging therapy is expected to be better [33–37]. However, there are no available data regarding minimal number of ECMO transports to be performed by the mobile teams to gain mandatory experience. Most publications included small cohorts of transported patients. Only in sixteen of them, a number of transports were exceeding 50, with 11 above 100. Of note, in one Swedish center, their number exceeded 900 [25]. In our study, only 12 patients have been transported between hospitals in the few last years. However, our experience gained in the cardiac surgery department regarding cannulation of the peripheral veins and arteries for extracorporeal circulation and security measures developed for in-hospital transport has resulted in the favorable results of ECMO-supported patients transfer, in spite of relatively low number of transportations.

4.2. Hub and Spoke. In order to achieve early and late optimal outcomes, it is necessary to bring the patients to centers with comprehensive and advanced treatment. The concept of "HandS-Hub and Spoke" was introduced by Combes et al. [33]. Safe patient transfer is a necessary bridge between ECMO centers and reference hospitals specialized in the conventional therapies, but also those that can initiate ECMO support [2]. The availability of beds will depend on capacity, mode of transport supported (ground and air), physical and geographical location, and the number of inhabitants of a given area. Patients who require ECMO support can be transferred to a large-volume center by a mobile ECMO team. Bearing in mind the risk of seasonal viral infections such as AH1N1 influenza and SARS-Cov-2, particularly in the aging societies with comorbidities, a temporary need for the use of this aforementioned support is important. Broman et al. suggested that, for the treatment of respiratory failure among the three age groups (neonatology, children, and adults), one ECMO center per 5–10 million population should be prepared whereas for the adults only one should be prepared per 8–15 million, respectively [34].

The international experts have suggested that transport of unstable refractory respiratory patient is safer when being on ECMO than when being conventionally ventilated [35, 36]. Brechot et al. in a retrospective single center study that involves 118 transfers confirmed the safety of patient ECMO transfer. Moreover, the results of these patients were comparable with the outcomes of patients in whom ECMO support was carried out in the ECMO center, without any transfer [25].

The authors of this article have developed a pioneer regional ECMO program in Poland: "ECMO for Greater Poland" in 2016. The intention was to create algorithms and improve the coordination of Medical Rescue Teams in the "ECMO rescue chain." Previous simulation-based training allowed building a successful procedural chain and then eliminating errors at various stages in identification, notification, transportation, and ECMO support [32].

4.3. Transport Definition. It is a combination of classical transfer of critically ill persons (suffering from failure of at least one organ or system), often mechanically ventilated, receiving continuous infusion of drugs and/or treated by means of extracorporeal circulation (ECC). Transporting them during ECMO support is very demanding due to the high complexity, chronic shortage of time, and environmental pressures. Expert consensus indicates that each ECMO network should have an appropriate ECMO Mobile Team [33, 38].

The "ground time," the period of necessary resuscitation/stabilization and careful observation after ECMO support initiation, switching over to the transport unit's equipment, and before leaving the reporting unit, may last up to 5 hours [39]. A special attention must be paid to identify any potential problems that may appear during transportation. ELSO has already issued guidelines for transportation to assist in the most appropriate vehicle selection [2]. The time from the initial qualification of any patient by ECMO physician to the bedside assessment at the call point should be as short as possible [18].

A primary transport is defined if the mobile ECMO team performs the cannulation of the patient and initiation of therapy at the referring hospital and then supervises transfer to an ECMO center [2,37]. A subtype of primary transport is when the mobile team initiates ECMO support at the regional hospital, but placement of the cannulae is performed by the referring to hospital's physicians. A transport is defined as secondary if the patient had already been on extracorporeal support but the mobile ECMO team supervised only transfer to the Center of Excellence [39].

4.4. Transportation Vehicle

4.4.1. Ground Transport. It is a complex logistics task to plan, control, and implement optimal transport strategy (in ELSO recommendation, up to 400 km (250–300 miles)) [2]. When properly prepared, it should be repeatable and simple to carry out. All centers included in the study used the land route. For the purpose of ECMO transport, it is necessary to equip the vehicle with an efficient 230V installation, capable of securing the power supply of electrical devices with a safe power reserve. Above-standard and energy-consuming devices such as the ECMO pump and heat exchanger should be taken into account. It is also necessary to provide a supply of medical gases capable of covering the needs of mechanical ventilation devices and an oxygenator. This requires prior planning of the length and time of the journey, assuming that the gas reserves should cover twice the time estimated for the transport. The patient can usually be accessed from at least three sides. Equipment can be attached to stretchers, handles, or mounting rails installed in the medical compartment. Having in mind all aforementioned requirements of optimal ECMO ground transport, members of our team actively participated in equipping of the special ambulance dedicated for critically ill patients. Possessing such ambulance, our team felt comfortable; thus, all our transfers were done by ground transport.

The key requirements of mobile intensive care units (MICU) equipment are difficult to standardize and they differ from country to country. Typically, it is a C-type ambulance adapted to carry more medical devices, equipped with additional power supply, ventilation, suspension, and a patient transport system, as shown in Figure 2. With regard to the current conditions in the Republic of Poland, there is no systematic mobile intensive care program, and the availability of this type of transport with a qualified team is negligible and depends on the internal arrangements of ECMO centers [32]. Yeo et al. reported the possibility of transport without the use of an advanced respirator, replacing it with a self-inflating bag. Ventilation was monitored with a portable device for analyzing critical parameters [18].

4.4.2. Air Transport. The use of air transport depends on its availability (the aviation team is in the hospital structure, having a hospital landing pad, local medical air transport policy, etc.) and terrain obstacles (ELSO recommendation for distances up to 650 km or 300–400 miles). Some centers have developed fixed-wing aircrafts transfers, mostly for international transportation [2]. Thirteen studies reported flights by airplanes, especially those used for long-distance transports [12–16, 19, 22–24, 26, 28, 30, 31]. Other centers have employed a "hybrid" transfer; the ambulance is placed inside a military plane, which allows it to avoid potentially risky displacement of the patient [30].

Air transportation may have the significant and unfavorable effect on the vital parameters of the patient, such as heart rate, systemic arterial pressure, and intracranial and stomach pressure [31]. Additionally, air missions are associated with exposure of both patient and medical staff to the 8 classic stressors such as hypoxia, changes in barometric pressure, temperature variations, reduced air humidity, noise, vibrations, and easier to tire and gravitational forces (overloads). The risk is associated with the occurrence of hypoxia and hypothermia resulting from the drop in atmospheric pressure and an increase in the volume of gas in physiologically aerated (e.g., sinuses) or not (e.g., pneumothorax, free air behind the eyeball) body spaces or equipment (intubation/tracheostomy tube cuff). However, taking into account the cruising altitudes of helicopters, the aspects related to pressure changes are irrelevant, and the hermetic cabin of the medical plane makes the issues of pressure changes negligible. Additionally, the forces of inertia (acceleration/deceleration) and vibrations of varying degrees are active [13–18, 31].

Furthermore, this transport mode does not always guarantee time savings (time-consuming organization) and thus should be used only on long and very long routes [12]. It can be also indispensable when moving the patient over difficult terrain or from places surrounded by water. The helicopter must use dedicated hospital landing pads and airports. Moreover, there is limited space for equipment and personnel which makes in-flight interventions much more difficult, even impossible (e.g., endotracheal intubation and full inspection of the ECMO system). There are also needs for a landing pad and bringing the patient to the airport with additional transport by ambulance required. Repeatedly moving patients from one point to the next with proper transfer protocols also poses possible risks such as inadequate supervision monitoring and timely interventions, as well as reliance on limited battery power and cylinder gases. Moreover, the economic aspects of such missions should also be taken into account.

4.4.3. ECMO Mobile Team. None of the guidelines have defined the minimum personnel composition of the mobile ECMO team and therefore each of the centers developed its optimized concept [2]. Depending on the legal and organizational conditions of a given country, different competences, duties, and local traditions, the number of its members can be different. Mobile team should be capable of professionally treating a patient with critical cardiopulmonary failure refractory to conventional therapy. Additionally, the availability of such services should be possible at all times. The relevant scope of competence should include experience in critically ill patient transportation, skills in cannulation, and ECMO system support as well as patient care.

There are general recommendations for qualified medical professionals including physicians, transport specialists, nurses, perfusionists, and other ECMO specialists [4]. When analyzing the selected scope of literature in terms of the personnel involved in transport, in Bonn model, the minimal number of staff is two and consists of anesthetic nurse and anaesthesiologist [28]. It should be noted that in this case the ambulance (driver-rescuer and lifeguard) or the aircraft team (commander, pilots, and others) tasked to

Table 1: Summary of our experience with transfers of the ECMO-supported patients.

No.	Sex	Age (years)	ECMO type	Cannulation	Vehicle	On ECMO transportation distance (km)	Indication	Deaths or incidents
1	F	56	VV	Percutaneous	AC	120	RRF	—
2	F	19	VV	Percutaneous	AC	10	RRF	—
3	M	52	VV	Percutaneous	AC	10	RRF	—
4	M	59	VV	Percutaneous	AC	40	RRF	—
5	M	28	VV	Percutaneous	AC	50	RRF	—
6	M	2	VV	Percutaneous	AD	200	RRF	—
7	M	21	VA	Surgical	AD	80	CS	—
8	M	63	VV	Percutaneous	AD	120	RRF	—
9	F	23	VV	Percutaneous	AD	5	RRF	—
10	M	19	VV	Percutaneous	AD	10	RRF	—
11	F	38	VV	Percutaneous	AD	100	RRF	—
12	F	62	VV	Percutaneous	AD	5	RRF	—

*Median with range (minimal/maximal values); AC: conventional ambulance; AD: ECMO-dedicated ambulance; CS: cardiogenic shock; ECMO: extracorporeal membrane oxygenation; RRF: reversible respiratory failure; VV: venovenous; VA: venoarterial.

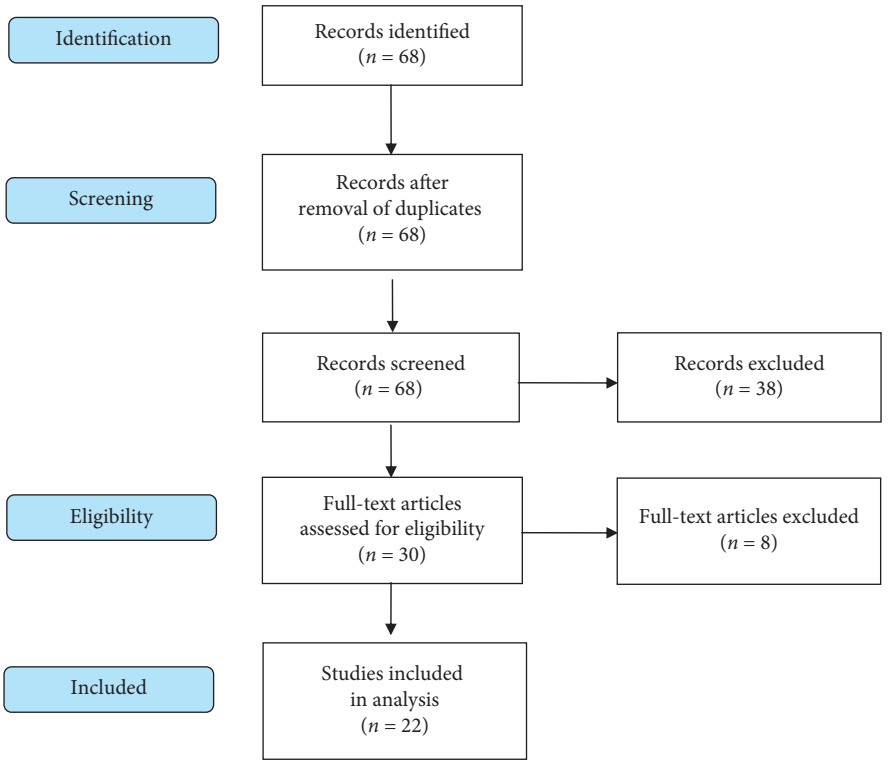

Figure 1: Research flowchart according to PRISMA statement.

handle transport and equipment does not constitute the ECMO team per se. The ECMO Karolinska Transport Service team usually includes 3 to 4 persons [33] including the ECMO physician, intensive care nurse with ECMO competences (called ECMO specialist), and surgeon with experience in adult and pediatric thoracic surgery. The operating nurse may join such team for international transports as decided by the surgeon. Ericsson et al. proposed abandoning the models with strictly defined roles so as to optimize effectiveness and safety. The ECMO specialist and physician should have full competence and authorization to operate the system and its components [39]. In most centers (including ours), the ECMO circuit is primed by a perfusionist but in the other centers this may be accomplished by physician or nurse after completion of education courses. Depending on center preferences, the cannulation is performed through surgical access or percutaneously [11–33].

Mobile ECMO team developed in "ECMO for Greater Poland" program consists of two critical paramedics, perfusionist, cardiac surgeon, and intensivist. That team is prepared to evaluate the patient and ECMO indication, introduce ECMO cannulas to the dedicated vessels, perform prime of the extracorporeal device, and initiate and manage

Table 2: List of included studies. General information, reported transfers, vehicle type, incidents and deaths, distance, and ECMO team persons.

Author	Year of publication	Center	Reported period	No. of transfers	Transfers (month)	Transfer types		Vehicle (%)		Incidents (%)	Deaths	Distance (km)		Type of support	No. of ECMO team persons
						Primary	Secondary	Ground	Air			Min	Max		
Roch A. et al. [11]	2013	Marseille	48	85	1.8	85	0	100	0	0	0	xx	xx	VV	3
Bryner B. et al. [12]	2014	Michigan	240	221	0.9	221	0	69	30	13	1 (*R*) 5 (*N*)	xx	xx	VA, VV	3
Sherren P.B. et al. [13]	2015	London	12	47	3.9	47	0	98.4	1.6	2	1 (*N*)	3.7	550.3	VV	3
Vaja R. et al. [14]	2015	Leicestershire	60	102	1.7	102	0	77	22	1	0	5.8	1576.8	VA, VV	4
Raspe C. et al. [15]	2015	Halle	36	36	1.0	36	0	33	64	0	0	3.5	115.0	VV	3
Salna M. et al. [16]	2017	NY Presbyterian	105	222	2.1	175	47	98.2	1.8	0	0	3.7	11398.2	VA, VV	6
Uribarri A. [17]	2017	Salamanca	33	9	0.3	2	7	100	0	0	0	126.0	224.0	VA, VV	4
Yeo H. J. et al. [18]	2017	Yangsan	46	18	0.4	18	0	100	0	0	0	26.0	408.0	VA, VV	5
Guenther S.P.W. [19]	2017	Munich	40	40	1.0	40	0	72.5	27.5	0	0	5.6	116.4	VA	2
Cianchi G. et al. [20]	2017	Florence	87	91	1.0	91	0	100	0	0	0	5.0	407.0	VV	4
Mendes P. V. et al. [21]	2017	São Paulo	48	7	0.1	7	0	86	14	xx	xx	0.5	163	VV	4
Blecha S. et al. [22]	2018	Regensburg	20	52	2.6	52	0	67.8	32.2	11.8	0	23.0	105.0	VA, VV	3
MacDonald M.D. et al. [23]	2018	Philadelphia	36	79	2.2	75	4	39	61	1.0	1 (N)	4.8	165.7	VV	4
Heuer J.F. [24]	2018	Bochum	60	75	1.3	75	0	55	45	0	0	24.4	207.6	VV	3
Brechot N. et al. [25]	2018	Paris	48	118	2,5	118	0	100	0	7.6	1 (R)	6	25	VA, VV	2
Austin D. E. et al. [26]	2018	Sydney	108	164	1.5	130	34	58	42	7.3	0	16.0	1908.0	VA, VV	2
Dalia A.A. et al. [27]	2019	Boston	84	51	0.6	0	51	100	0	xx	xx	xx	xx	VA	xx
Ehrentraut S.F. et al. [28]	2019	Bonn	120	126	1.1	126	0	85	15	6.3	4 (N)	7.0	548.0	VA, VV	2
Bonadonna D. et al. [29]	2019	Durham	24	132	5.5	132	0	100	0	0	0	xx	xx	VA, VV	4
Wilhelm M.J. et al. [30]	2019	Zurich	88	58	0.7	49	9	40	60	0	0	3.0	225.0	VA, VV	3

Table 2: Continued.

Author	Year of publication	Center	Reported period	No. of transfers	Transfers (month)	Transfer types		Vehicle (%)		Incidents (%)	Deaths	Distance (km)		Type of support	No. of ECMO team persons
						Primary	Secondary	Ground	Air			Min	Max		
Fletcher-Sandersjoo A. et al. [31]	2019	Karolinska	78	908	11.0	800	108	40.3	59.3	20.0	2 (R)	6.9	13447.0	VA, VV	2
Puslecki M. et al. [32]	2019	Poznan	36	6	0.2	6	0	100	0	xx	0	3.0	200.0	VA, VV	4

VV: venovenous; VA: venoarterial; R: related; N: not related.

of all aspects of critically ill patient treatment, including the ECMO circuit, ventilation, medications, and anticoagulation. Additionally, they are trained and prepared for urgent intervention to resolve possible and not uncommonly life-threatening complications [32].

4.4.4. Equipment. Some of the devices including anticoagulation monitoring (i.e., ACT analyzer) and additional surgical equipment (sterile instruments, sutures, dressing, and head lamps) or transportable ultrasound should be secured by self-sufficient mobile ECMO team. Additionally, it is recommended to double the sterile equipment because they are usually not available at the referring hospital. Obviously, manual or backup power ECMO supply, spare emergency ECMO circuit, connectors, extra pump head and oxygenator, and spare cannulas should be provided.

To save time from activation to departure for the patient, the teams use preprepared kits signed bags that are regularly checked for completeness and expiry dates, as shown in Figure 3.

Equipment verification is done using a checklist to avoid missing essential items. The team's equipment proposal is included in Appendix 1 in Supplementary Materials. However, the autonomy of a given center in terms of equipment is recommended [2, 3, 39, 40].

Mobile ECMO teams maintain their readiness round the clock, often with varying lengths of response time during the day and during the night. Taking into account the key aspects of reaching the qualified bedside assessment as quickly as possible, transport teams regularly check the completeness and efficiency of the equipment elements.

4.4.5. Checklists. A standard operating procedure (SOP) is a set of established steps and rules that must be followed until a desired state of affairs is achieved. It gives control over the course, supports situational awareness, and prevents overlooking important elements. SOPs have their source in the aviation community and prehospital medicine and battlefields are drawn from them. Standardized equipment preparation and sequence of operations are crucial in avoiding human error by improving intrateam communication and patient safety [41]. From the psychological perspective, demanding and stressful circumstances may significantly disturb situational awareness [42]; hence, there is a necessity to provide help in the forms of checklists. Emergency procedures without purpose and plan put unnecessary risk on both professionals and patients [43–45].

The procedures and checklists are divided into (a) clinical key actions taken before and during the transfer and (b) hardware/logistics such as equipment, notification algorithms, and organization. Checklists and standard procedures were adapted from aviation, where there was a panacea for increasing crew requirements and increasing complexity of aircraft. The case of Elaine Bromiley in 2005, who was severely mutilated during induction for routine surgery as a result of a series of crucial actions, is also often mentioned. Her husband (a professional pilot) decided to promote among the medical professions a procedural approach adopted from aviation [43, 44]. A breakthrough moment for modern medicine was the introduction by the International Health Organization, the perioperative control card, which significantly reduced the number of complications in the operational fields [45].

In the concept phase of the "ECMO for Grater Poland," a review of the literature and available materials published by the other experienced ECMO centers were included. On their basis, in combination with high-fidelity simulations [32], an owned adaptation of checklists and hardware as the result of innovation cooperation of all parties involved, presented below, was developed. During the summary, SOPs were constantly evaluated and adapted to the changing needs, requirements, and possibilities. The following innovation procedures and checklists have been developed for the ECMO transport team:

(1) "Prequalification card": an idea of creating this card is to provide the ECMO coordinator for analysis with the necessary diagnostic data (e-mail and fax) in order to identify the need for extracorporeal therapy. Additionally, it contains the basic equipment and logistic requirements recommended in the reporting center (access to gas, electricity, etc.).

(2) Procedure "arrival": this is procedures for the ECMO and regional Emergency Medical Service (EMS) coordinators that support the decision-making and logistic process of transport organization.

(3) Checklist "equipment": this is the list of necessary equipment to be completed and reviewed prior to departure to the reporting center that is divided into "perfusion" and "intensive" equipment.

(4) Procedure "with the patient": it presents the steps that are taken by ECMO coordinator such as bedside assessment and final decision on possible ECMO therapy and its type (VV and VA), by nursing and ECMO team. The purpose of this document is to provide the appropriate forces and resources and to maintain the correct sequence of actions.

(5) Procedure "departure with the patient": this is the most demanding of the stages. A role of this document is to pay close attention to the division of roles of team members involved in cooperation to secure energy and gas reserves and to reach safely the means of transport.

4.4.6. Outcomes. In our systematic review, only 15 deaths out of 2647 adult patient transfers were reported,11 deaths associated with cannulation but not directly to transportation and only 4 (0.15%) directly related to medical transfers. Well-prepared and experienced teams guarantee safe long- and short-distance interhospital transports when being on ECMO support.

The factors that accompanied deaths were the critical condition of the patient [12, 25, 31]. The very good aforementioned results regarding transport-related mortality may result from high qualifications of team members, accurate selection of patients, type of support, means of transport,

meticulous assessment, and reporting the patient to a reference center at optimal time. In our relatively small owned experience of 12 transfers, all of them were uneventful.

4.4.7. Adverse Events. Unfortunately, high-risk or life-threatening situations may occur. The necessary immediate interventions must be taken within seconds and they demand highly trained personnel. In Broman and Frekman at adverse events or complications during ECMO transports, the incidence of any kind of them occurred in 31.7% cases [37]. In the recent Karolinska center paper that involved 908 transportations, the complication rate was found to be 20% [31]; Table 3 includes percentage of adverse events in single center publications [31, 37, 39].

In 6.2% critically ill subjects, more than one complication was reported [5, 37]. Most common events were related to the patient's clinical status (28.2%), of which loss of tidal volume accounted for 11.5%. Equipment-related problems can occur in 5–8%. Others were unforeseen but reported adverse events were hypothermia, intravenous lines freezing, and traffic accidents. Authors of this review in their previous paper revealed the lack of knowledge and adaptation by the ambulance service that exposed both patient and medical team to risk in 4% of the transports [6, 37]. The most experienced specialist teams dealing with critical transfers during ECMO therapy followed the procedures and protocols and created adverse events catalogs that occurred in the transport-related situations. Fletcher-Sandersjoo et al. reviewing next 586 transportation in Karolinska center have come up with the following categorization [31]:

(I) High risk for morbidity and mortality without response within seconds

(II) High risk for morbidity and mortality with no response within minutes

(III) Need of attention, with no risk to morbidity or mortality

(IV) Low risk needed to be noted

Categories I and II were observed in 20% of the actions, but they had no impact on mortality (Table 3). The greatest risk (occurrence of category I and/or II adverse events) was noticed during the flights in airplane and when applying VA ECMO. Moreover, secondary transfers were associated with greater risk; therefore, special attention and a greater number of specialists should be taken. The estimated probability of adverse events was 28%. As remedial actions after the occurrence of I and II events, it was proposed to create a checklist, introduce professionals to the teams, and improve interpersonal communication.

Adverse events most often were related to such aspects as equipment failure, improper preparation (training deficiencies and insufficiencies and inadequate equipment), insufficient documentation, and suboptimal communication [31]. Despite the occurrence in 20% of transfers of situations defined as threatening within seconds or minutes (I and II), no significant statistical impact was recorded due to the observance of the rules of organization and implementation of such projects (professional, equipped team). Moreover, the review of these events resulted in a revision of the current procedure and the creation of remedial measures for the future. The issue of "tidal volume loss," according to Broman, is debatable due to the conventional ventilation strategy. After starting ECMO, the parameters of the ventilator for lung-protection ventilation were modified, which may cause false results and may be perceived as an adverse event. The decreasing number of incidents in Karolinska team proves the increase in team skills and transport safety.

The researchers also made comparisons between groups of patients supported with ECMO and then transported vs treated with ECMO inpatient without any transfers between hospitals [28]. The reports showed no statistically significant differences in terms of survival. Salna et al. have shown that the patients cannulated by the mobile teams experienced better outcomes than those cannulated by the referring hospital medics. The fact that clinical status of individuals cannulated on-site was much worse cannot be excluded; thus, physicians must not wait for mobile team arrivals and faster actions were obligatory [16]. The type of therapy, VV or VA, also had no significant impact of eventual outcomes but subjects undergoing VA therapy can require more urgent interventions during the transfer. However, due to different indications comparisons VV versus VA ECMO applications must be done very carefully and cautiously.

4.5. ECMO Transportation in Poland as an Innovative Multidisciplinary Cooperation. Extracorporeal techniques in the Polish intensive care units are not routine procedures. Apart from exceptional centers in Poland where such treatment is provided due to local initiatives, there is no systemic cooperation solution in Poland that would ensure universal access to this therapy (as it requires involvement of a lot of parties, as well as unique knowledge, skills, competences, and desired experience). There are no confirmed epidemiological data regarding use (exact numbers and places) of VV-ECMO systems. More information is available on VA-ECMO therapy as they are implemented and obligatory reported to the central registry by cardiac surgical departments.

Consequently, a real need for this type transfers in Poland is difficult to estimate due to formal and organizational problems, shortages of places in higher-reference centers, and difficulties in rationally escalating the therapy, without omitting the currently strongly recommended interventions. Moreover, many individuals that would potentially benefit from ECMO support are not referred to expert centers.

Most world leading ELSO institutions have already implemented the concept of "hub and spoke," where specialized transport of patients to the center of reference plays a fundamental role. Despite lack of dedicated ECMO centers in Poland, the Polish Guidelines issued by the National Intensive Care Consultant and VV-ECMO therapy team recommended protocols and procedures for the mobile ECMO teams' assessment, notification, and ECMO implementation before transfer that patient to the high-volume

Figure 2: Ambulance used to transport critically ill patients in "ECMO for Greater Poland" program.

ECMO center. The "HandS" conception has been realized in 6 centers (Zabrze, Cracow, Lublin, Warsaw, Opole, and Poznan) with dedicated transportation teams. Pediatric transfer in Poland is marginal. There are individual case-study reports.

"ECMO for Greater Poland" is the nation's first regional program implementing extracorporeal support for 3.5 million inhabitants of the Greater Poland region (with Poznan the capital city) especially in patients with severe reversible respiratory failure (RRF), hypothermia, and critical states resulting in heart failure due to cardiac arrest, cardiogenic shock, or acute intoxication and promotion of donor after circulatory death (DCD) strategy in selected organ donor cases, after unsuccessful lifesaving treatment, to achieve organ recovery. It is significant that, before launching the program with dedicated transport, the ECMO support application in this region was incidental [32].

The aim of the "ECMO for Greater Poland" program is to create system-wide procedures for the identification of potential candidates for extracorporeal perfusion and their transport to specialized medical centers, in order to implement and conduct therapy at the highest possible level. It may be possible thanks to the improvement of the disposition and coordination of the Medical Rescue System, appropriate qualifications of the medical personnel of Emergency Departments and selected intensive care units, creation and specialized training of resuscitation, and perfusion and transplant teams.

The role of the hub is the integration of external partners, coordination of innovative cooperation, knowledge transfer and diffusion of knowledge, monitoring, management and control of the ecosystem, and continuous improvement of existing procedures, qualifications, and skills within a dedicated educational platform in order to develop mutual competencies necessary in the development of new therapies for patients [46], as shown in Figure 4. This cooperation enables a number of innovative projects and allows significant synergy effects and helps in getting easier response to changes in the environment (COVID-19 pandemic). The involvement of all partners, from both local and regional levels, from business and academia, in the cooperation, can have a positive effect on innovation cooperation performance of the whole "ECMO for Greater Poland" innovation ecosystem [47]; also, it can enable the development of new modes of cooperation [48, 49], including, for example, R&D alliances, Open Innovation alliances, cross-industry alliances, and altruistic alliances.

Since the end of the 1980s, we can observe more and more nonequity R&D alliances in the biopharmaceutical industry in the world [48], which provide greater flexibility in the selection and possible change of partners and also enable a faster change or exchange of technology than traditional equity alliances. This trend can also be seen in the region of the Central and Eastern Europe (CEE). The results of one of the first in the world qualitative and quantitative primary research focused on innovation cooperation in the biopharmaceutical industry in the CEE region, conducted within research grant entitled "Analysis of Open Innovation Alliances and Strategic Partnerships in the Biopharmaceutical Industry in Poland and CEE Countries," showed that over 80% of companies ($n = 107$) from the biopharmaceutical industry from 18 CEE countries carried out mainly R&D nonequity alliances in the development of innovation cooperation in years 2015–2017. However, only 18% of them have implemented innovation cooperation using new modes of cooperation, Open Innovation alliances. It should be also taken into account that more than 65% of companies are open to develop cross-industry alliances and altruistic alliances (nonprofit) with companies or institutions in the biopharmaceutical industry and in other industries. With more flexible modes of cooperation, it is possible to deliver new solutions and patient treatment faster, using the innovative potential of all partners involved in the cooperation in the "ECMO for Greater Poland" program.

The ECMO mobile team was created on a voluntary basis. Thanks to the launch of the program, emergency teams in the region were equipped with 15 mechanical

Table 3: Sources of adverse events according to the typology of Broman et al. along with the percentage distribution after detailed analysis of 322, 514, and 908 transfers.

Sources related to	Karolinska (322 transfers) 94 incidents [37] (%)	Karolinska (514 transfers) 206 incidents [39] (%)	Karolinska (908 transfers) 252 incidents [31] (%)
Patient	70.0	65.0	62.0
Equipment	17.0	14.6	19.0
Vehicle	7.4	12.6	13.0
Environment	3.1	1.9	2.0
Personnel	2.1	5.8	5.0

Figure 3: Transport bag for ECMO device.

compression devices and one dedicated ambulance for transport of ECMO-supported patients [50]. Up to now, 12 uneventful transfers of ECMO-supported patients have been performed in the last 4 years.

It is difficult to estimate the demand for extracorporeal techniques, taking into account epidemiological needs. According to German estimates, in the corresponding population, the number of cases of severe RRF may reach 8–10 patients per million inhabitants per year. This is a significant number of patients who can be treated by applying these techniques and in the experienced centers the survival rate can be as high as 70% [51]. Of note, the most sophisticated respiratory techniques may be associated with only 10–20% survival rate [52]. VA therapy seems to be more demanding and should be concerned for use in the states of severe cardiorespiratory failure or resuscitation of various etiologies. This may also include critically ill young patients waiting for organ transplants (heart and lung). In such situations, maintenance of vital functions in the form of ECMO should be initiated in the regional hospital and then subjects should be transported to a transplant center. Extracorporeal circulatory support techniques used in the cases of end-stage heart failure are recognized therapeutic form of mechanical circulatory support and transplantation programs as "bridge to decision" or "bridge to bridge" [53].

4.6. ECMO Transportation in Poland in COVID-19 Pandemic. Despite the lack of dedicated ground ECMO transportation system in Poland, the COVID-19 pandemic resulted in the creation of 5 dedicated centers for VV-ECMO support in COVID patients (Lublin, Warsaw, Cracow, Gdańsk, and Wroclaw). The developing epidemic provoked the initiative of air transportation (HEMS: Helicopter Emergency Medical

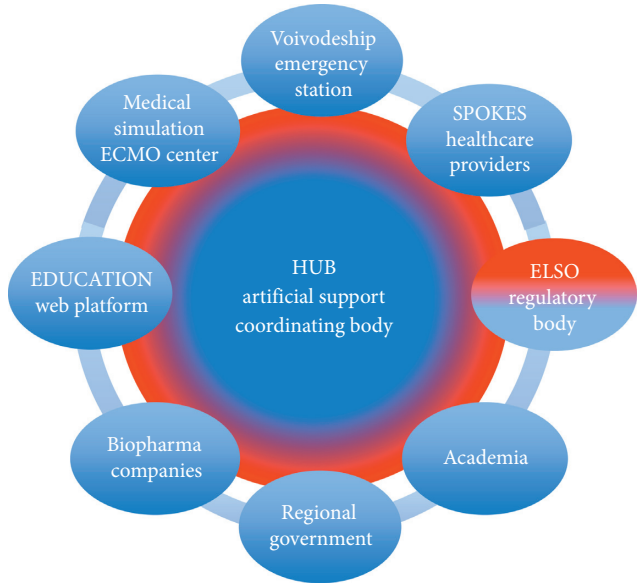

Figure 4: "ECMO for Greater Poland" Innovation Ecosystem.

Service, helicopters and planes) in Poland, and for several months transport by helicopter has been available 24 hours a day in five Polish HEMS stations. During last months, few ground and air COVID patients with ECMO support were performed. In HEMS, there is one dedicated device, Cardiohelp (Getinge, Rastatt, and Germany), which has been registered under the Polish aviation regulation (without heater).

"ECMO for Greater Poland" mobile ECMO team recently performed one transfer with COVID suspected patient with ECMO-dedicated ambulance. Transfer and ECMO implantation were properly prepared with developed checklists, including team division in "cold" and "hot" zone and personal protective equipment use. For the purposes of precise separation of units and equipment, rational use of PPE, and to prevent contamination of the equipment and transport bags, an additional vehicle (for not contaminated bags and devices) with a driver was provided. The transport went without unexpected complications.

4.7. Role of Translational Simulation in ECMO Transportation. Translational simulation is a term describing the part of simulation activities focused on improving healthcare processes and outcomes [54]. It can be realized through diagnosing safety and performance issues as well as delivering simulation-based intervention, irrespective of the location, modality, or content of the simulation. Translational simulation can be an improving safety in ECMO transportation. We must remember that result depends on the frequency and preparation of the team and the circumstances under which the patient transfer occurs. High-fidelity medical simulations give opportunity to create and test procedures and checklists developing situational awareness and entrusting such tasks to specialized teams, prepared and trained in a given field [49].

In support of the validity of the simulation education in ECMO transfers, a review of the methods used in the world was the part of Broman et al.'s survey [39]. 14 of 15 centers performed some kind of structured training: five (33%) combine ECMO clinical and ECMO transport training (i.e., simulations and rescue training aircraft); nine centers (60%) perform regular ECMO simulations and 3 centers (20%) perform annual transport simulations. 4 others perform ECMO pump training and in-house simulations. An overview of identified simulation techniques includes the following:

(i) high fidelity simulations - ground and air;
(ii) wet labs, sims;
(iii) not formal certified workshops;
(iv) online trainings and no sim in vehicles;
(v) aircraft in vehicle sim - yearly training;
(vi) ECMO transport simulation in vehicle sim - twice in year.

The "ECMO for Greater Poland" program uses, as a superior, proprietary tool allowing the flexibility to create previously nonexistent procedures, high-fidelity simulation. It allows for high-quality personal and procedural training in an accessible and repeatable way. In the case of rare, complicated, and expensive procedures, it allows for "probing" standardized and repeated training, skills' improvement, and their verification. In addition, it allows for improving Healthcare Service, communication for best patients' outcomes [53]. The role of medical simulation in the educational process is invaluable and still underrated. The economic result of simulation training is an optimized cost of improving theoretical and practical skills.

In "ECMO for Greater Poland" program, high-fidelity simulation scenario of patient (mannequin) transfer with

implanted ECMO console for mobile ECMO team was created. A 80 km transfer via road ambulance between two cities was performed. During transportation, all critical patient parameters were under meticulous control. Moreover, the efficacy of electrical sources and oxygen supply mandatory for the complex procedure was also confirmed. This probing simulation allowed us to control the deployment of qualified medical personnel and to know about necessary equipment in the ambulance. In addition, proprietary equipment lists and checklists for the individual stages of transport were created. In addition, the experience of first 5 transports in the standard ambulances allowed for designation and raised funds for the container ambulance dedicated for ECMO transport (the first ECMO ambulance in Poland).

4.8. Artificial Life Support with ECMO. "ECMO for Greater Poland" also has an educational intention and we have developed a course about "Artificial Life Support with ECMO" and created the "Center of Artificial Life Support and Patient Safety" within a University Medical Simulation Center. The project will be implemented in 2019–2021 at the Medical University of Karol Marcinkowski in Poznan. The project was awarded funding from a POWER competitive national grant (POWR.05.04.00-IP.05-00-006/18) by the Polish Ministry of Health for a total of 2,750,000 USD (PLN 10,974,708.60).

The program is offered to 264 physicians from Poland specializing in anaesthesia and intensive care, cardiac surgery, cardiology, thoracic surgery, vascular surgery, transplantology, and emergency medicine and other physicians in training from all over Poland. An important part of educational 3-day program is the ECMO transportation subject with lectures, transfers checklist creation, and intra- and interhospital transfers simulation scenarios. Since 2019, 154 physicians from Poland have finished the ELSO endorsed course. Moreover, 2 in 10 trained simulation scenario lists include intrahospital and interhospital ECMO patient transfer in ambulance vehicle training in Center of Medical Simulation.

ECMO team and ECMO mobile time of "ECMO for Greater Poland" program offer training twice in year interhospital ground transfer in vehicle simulator in the Center of Medical Simulation.

4.9. Controversies in Previous Publications and Limitation. There is a problem with accurate estimation of the ECMO transfer numbers, deaths, or undesired incidents on the basis of previously published reports because they often counted also conventional transportation. The authors reviewed the publication critically, selecting from a given center reports with most actual and containing the highest number of transports performed. In addition, the meta-analysis eliminated conventional transports from the total number.

This work does not include the transport of ECMO-supported patients with symptomatic COVID-19. All included reports had been published before the end of 2019.

We believe that this is the first analysis that captures previously repeated errors in the estimated number of transports and deaths. There should be an extended analysis of the hospital survivors of transferred patients with ECMO support following on from this.

5. Conclusions

The ECMO transportation of critically ill patients is a complex demanding procedure and process but it can be performed safely by well-trained and cooperating dedicated ECMO team. Key aspects of transportation include the importance of "ground time" in primary transfers, dedicated vehicle, and dedicated ECMO mobile team. Checklists and standard operating procedures are important to create safe environment for the patient and team. The valid ELSO recommendations regarding ECMO transportation are important guidelines. However, in each center it is necessary to develop individualized transfers protocols. Due to its complexity, involvement of many medical professionals, and numerous possible serious adverse events, the role of "probing" medical simulations to check on regular basis the personnel qualifications is extremely important to ensure safety of transfer of ECMO-supported individuals. We have therefore leveraged on a HUB innovation ecosystem to support the safety of the treated patients with extracorporeal support.

Abbreviations

ECMO: Extracorporeal membrane oxygenation
ELSO: Extracorporeal Life Support Organization
COVID-19: Coronavirus disease
RCT: Randomized control trial
VV: Venovenous
VA: Venoarterial
HandS: Hub and Spoke
RRF: Reversible respiratory failure
DCD: Donor after circulatory death
SOP: Standard operating procedure
ACT: Activated clotting time
PEEP: Positive end-expiratory pressure
ECG: Electrocardiography
SpO2: Pulse oximetry.

Data Availability

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

Ethical Approval

According to the rules of Local Bioethical Committee of Poznan University of Medical Sciences, ethical approval is not required for retrospective documentation research and literature research, and therefore, no formal ethical approval was required.

Disclosure

The authors alone are responsible for the content and writing of this paper.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Conceptualization of the simulation scenario was done by MP, KB, MD, and KB; conceptualization of the "ECMO for Greater Poland" innovation ecosystem was performed by LP and MP; mobile ECMO team included MP, MD, ML, SS, and AP; MZ, EG, PM, and TK; publication review was made by LP, LS; RP, BP, and MJ; checklists proposal was made by MP, MD, KB, ML, and BP; literature research was achieved by MP, MD, KB, ML, BP, LP, SS, and AOW. All authors have read and agreed to the published version of the manuscript.

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Supplementary Materials

Appendix 1: the mobile ECMO team's equipment proposal for "ECMO for Greater Poland" program. (*Supplementary Materials*)

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Research Article

Response Time Threshold for Predicting Outcomes of Patients with Out-of-Hospital Cardiac Arrest

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Ambulance response time is a prognostic factor for out-of-hospital cardiac arrest (OHCA), but the impact of ambulance response time under different situations remains unclear. We evaluated the threshold of ambulance response time for predicting survival to hospital discharge for patients with OHCA. A retrospective observational analysis was conducted using the emergency medical service (EMS) database (January 2015 to December 2019). Prehospital factors, underlying diseases, and OHCA outcomes were assessed. Receiver operating characteristic (ROC) curve analysis with Youden Index was performed to calculate optimal cut-off values for ambulance response time that predicted survival to hospital discharge. In all, 6742 cases of adult OHCA were analyzed. After adjustment for confounding factors, age (odds ratio [OR] = 0.983, 95% confidence interval [CI]: 0.975–0.992, $p < 0.001$), witness (OR = 3.022, 95% CI: 2.014–4.534, $p < 0.001$), public location (OR = 2.797, 95% CI: 2.062–3.793, $p < 0.001$), bystander cardiopulmonary resuscitation (CPR, OR = 1.363, 95% CI: 1.009–1.841, $p = 0.044$), EMT-paramedic response (EMT-P, OR = 1.713, 95% CI: 1.282–2.290, $p < 0.001$), and prehospital defibrillation using an automated external defibrillator ([AED] OR = 3.984, 95% CI: 2.920–5.435, $p < 0.001$) were statistically and significantly associated with survival to hospital discharge. The cut-off value was 6.2 min. If the location of OHCA was a public place or bystander CPR was provided, the threshold was prolonged to 7.2 min and 6.3 min, respectively. In the absence of a witness, EMT-P, or AED, the threshold was reduced to 4.2, 5, and 5 min, respectively. The adjusted OR of EMS response time for survival to hospital discharge was 1.217 (per minute shorter, CI: 1.140–1299, $p < 0.001$) and 1.992 (<6.2 min, 95% CI: 1.496–2.653, $p < 0.001$). The optimal response time threshold for survival to hospital discharge was 6.2 min. In the case of OHCA in public areas or with bystander CPR, the threshold was prolonged, and without witness, the optimal response time threshold was shortened.

1. Introduction

Out-of-hospital cardiac arrest (OHCA) is defined as the termination of cardiac mechanical activity and subsequent cessation of blood circulation in a patient outside of a hospital [1]. Despite improvements in prehospital management and the use of automated external defibrillators (AEDs), only 10%–20% of the patients who experience OHCA survive to hospital discharge [2, 3].

Many prehospital factors might influence the outcomes of OHCA, such as location of OHCA, witnessed arrest, bystander cardiopulmonary resuscitation (CPR), initial cardiac rhythm, and level of post-resuscitation care [3–6]. The emergency medical service (EMS) response time is defined as the time interval between the call made to the EMS and the arrival of the EMS team at the scene. EMS response time is a key prognostic factor for OHCA, and many studies have shown that short EMS response time is associated with a high probability of survival to hospital discharge and favorable neurologic outcomes [2, 7, 8]. On the other hand, patient-level characteristics, such as sex, age, and comorbidities, might also be prognostic factors of

OHCA [9–13]. However, the impact of patient comorbidities on the survival of OHCA patients remains controversial, and Andrew et al. showed that the presence of multiple comorbidities was independently related to a reduced probability of survival to hospital discharge [14]. However, Lai et al. found that cardiac comorbidities might be predictors of improved survival [11]. These results suggest that CPR/AED might be more effective for cardiogenic OHCA than for non-cardiogenic OHCA. Furthermore, the threshold of EMS response time for survival to hospital discharge after OHCA remains unclear. Patient-level differences and conditions of OHCA might influence the response time threshold. For example, Ono et al. found that bystander cardiopulmonary resuscitation (CPR) might prolong the response time threshold from 6.5 min to 7.5 min [7].

Hence, this study aimed to evaluate the EMS response time threshold for survival to hospital discharge for OHCA patients under different conditions, such as patient background and scene of OHCA. To achieve this, we used receiver operating characteristic (ROC) curve analysis and Youden Index.

2. Materials and Methods

2.1. Study Population. This study was conducted in Kaohsiung, with a population of approximately 2.77 million people, ranked as the third most populated city in Taiwan. The EMS data of OHCA patients were collected from January 2015 to December 2019. The EMS database has been described previously [2]. Briefly, EMS is a single-tiered fire department-based system, maintained by the Taiwanese government, and the data are stored electronically in every province's EMS command center. The EMS database consists of two parts. The first part includes demographic characteristics of the patients, such as age, sex, and comorbidities; details of the scene, such as bystander CPR and location of OHCA; and initial management, as recorded by emergency medical technicians (EMTs). The second part, including the outcome of OHCA patients and disposition, was completed by hospital reviewers. After reviewing the EMS database, we excluded patients aged <18 years [9], those who died due to trauma, cases of drowning, patients with "do not resuscitate" (DNR) orders or with incomplete data, and those transferred to other hospitals after initial resuscitation.

Demographic factors, such as age, sex, and comorbidities, initial management by EMTs, such as the use of defibrillation by automated external defibrillator (AED) or laryngeal mask airway (LMA), and details of the scene, such as bystander CPR and location of OHCA, were recorded in the EMS database. The study was approved by our hospital's institutional review board (number: 202001321B0) and was performed in accordance with the ethical standards set forth in the 1964 Declaration of Helsinki and its later amendments. Formal consent from the patients was not required for this type of study. The primary outcome was survival to hospital discharge.

2.2. Statistics. The results of the descriptive analyses of independent variables were presented as mean ± standard deviation (SD). The chi-square test, Mann–Whitney *U* test, and Student's *t*-test were used to analyze independent variables. Logistic regression was used to analyze the statistically significant relationship between prehospital factors, patient comorbidities, and the outcome of OHCA. The odds ratio (OR), 95% confidence interval (CI), and p values were also calculated using logistic regression. ROC curve analysis with Youden Index was then used to calculate the optimal cut-off value for EMS response time that predicted survival to discharge under different situations. A p value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 25.0 (IBM Corp, Armonk, NY, USA).

3. Results

A total of 10,933 cases of OHCA during the 5-year study period were recorded in Kaohsiung. We excluded patients aged below 18 years ($n = 128$); cases of burn, trauma, or drowning ($n = 1{,}619$); patients with DNR orders ($n = 1{,}216$); patients with missing outcomes or transferred to another hospital ($n = 564$); and patients with incomplete data ($n = 664$). Finally, 6,742 OHCA cases were analyzed in this study.

The demographic characteristics, comorbidities, and prehospital factors are listed in Table 1. A total of 224 OHCA patients survived to hospital discharge. Survival to hospital discharge was associated with young age ($p < 0.001$), male sex ($p = 0.014$), presence of witness ($p < 0.001$), public location of cardiac arrest ($p < 0.001$), provision of bystander CPR ($p < 0.001$), bystander airway support ($p = 0.001$), EMT-paramedic response ([EMT-P], $p < 0.001$), provision of initial shockable rhythm ($p < 0.001$), defibrillation by AED ($p < 0.001$), and short response time ($p < 0.001$).

Table 2 shows the findings of multivariate logistic regression of OHCA, adjusted for confounding factors of age, male sex, witness, EMS response time, cardiac arrest location (public), bystander CPR, bystander airway maintenance, EMT-P response, initial shockable rhythm, and prehospital defibrillation by AED. After adjusting for confounding factors, age (1 additional year, OR = 0.983, 95% CI: 0.975–0.992, $p < 0.001$), EMS response time (1 minute shorter, OR = 1.217, 95% CI: 1.140–1.299, $p < 0.001$), witness (OR = 3.022, 95% CI: 2.014–4.534, $p < 0.001$), public location (OR = 2.797, 95% CI: 2.062–3.793, $p < 0.001$), bystander CPR (OR = 1.453, 95% CI: 1.071–1.970, $p = 0.016$), EMT-P (OR = 1.713, 95% CI: 1.282–2.290, $p < 0.001$), and prehospital defibrillation by AED (OR = 3.984, 95% CI: 2.920–5.435, $p < 0.001$) were statistically and significantly associated with survival to hospital discharge.

Table 3 shows the results of the ROC curve analysis and the optimal response time threshold for predicting survival to hospital discharge. The overall response time threshold was 6.2 min. It was 7.2 min for OHCA occurring in the public area. For patients receiving bystander CPR or those aged <80 years [15], the response time threshold was 6.3 min. For cases without a witness, EMT-P response, and

Table 1: Demographic characteristics, comorbidities, and prehospital factors of 6742 medical out-of-hospital cardiac arrest patients.

Characteristics of medical out-of-hospital cardiac arrest (OHCA) patients	Survived to hospital discharge $n = 224$ (3.3%)	Did not survive to hospital discharge $n = 6518$ (96.7%)	p
Age (years)	60.9 ± 14.4	68.3 ± 16.1	<0.001
Male sex	162 (72.3%)	4190 (64.3%)	0.014
EMS response time (min)	5.8 ± 2.2	7.0 ± 3.2	<0.001
Witnessed arrests	192 (85.7%)	3872 (59.4%)	<0.001
Cardiac arrest location (public)	101 (45.1%)	1064 (16.3%)	<0.001
Bystander CPR	117 (52.2%)	2536 (38.9%)	<0.001
Bystander keep airway	27 (12.1%)	418 (6.4%)	0.001
Attended by EMS-paramedic	88 (39.3%)	1730 (26.5%)	<0.001
Initial shockable rhythm	34 (15.2%)	191 (2.9%)	<0.001
Defibrillation by AED	113 (50.4%)	875 (13.4%)	<0.001
Hypertension	89 (39.7%)	2284 (35.0%)	0.254
Diabetes	59 (26.3%)	1637 (25.1%)	0.807
Old stroke	19 (8.5%)	478 (7.3%)	0.617
Malignancy	15 (6.7%)	522 (8.0%)	0.41
Liver disease	10 (4.5%)	207 (3.2%)	0.326
Respiratory disease	12 (5.4%)	265 (4.1%)	0.401
Renal disease	25 (11.2%)	579 (8.9%)	0.3

Table 2: Adjusted odds ratios for survival to hospital discharge.

Adjusted odds ratios for outcome	Survival to hospital discharge		
Variables	OR	95% CI	p
Response time (one minute shorter)	1.217	1.140–1.299	<0.001
Age (one additional year)	0.983	0.975–0.992	<0.001
Male sex	0.901	0.653–1.245	0.529
Witness	3.022	2.014–4.534	<0.001
Cardiac arrest location (public)	2.797	2.062–3.793	<0.001
Bystander CPR	1.453	1.970–1.071	0.016
Bystander keep airway	1.022	0.638–1.636	0.928
Attended by EMT-Paramedic	1.713	1.282–2.290	<0.001
Initial shockable rhythm	1.542	0.986–2.411	0.057
Defibrillation by AED	3.984	2.920–5.435	<0.001

Table 3: Receiver operating characteristic (ROC) curve analysis of the optimal response time threshold for predicting survival to hospital discharge.

Situation		Survival to hospital discharge				
		Threshold (minutes)	AUC	Lower	Upper	p
Overall		6.2	0.618	0.582	0.654	<0.001
Witnesses	With	6.2	0.609	0.570	0.647	<0.001
	Without	4.2	0.643	0.544	0.743	<0.001
Cardiac arrest location	Public	7.2	0.628	0.576	0.681	<0.001
	Residence	6.1	0.611	0.563	0.66	<0.001
Bystander CPR	With	6.3	0.588	0.537	0.64	0.001
	Without	6.1	0.655	0.606	0.703	<0.001
Attended by EMS-paramedic	With	6.2	0.635	0.581	0.689	<0.001
	Without	5.0	0.605	0.558	0.653	<0.001
Defibrillation by AED	With	6.2	0.619	0.568	0.669	<0.001
	Without	5.0	0.632	0.572	0.675	<0.001
Age	<80 years	6.3	0.627	0.589	0.665	<0.001
	≥80 years	5.1	0.588	0.524	0.651	0.007

defibrillation with AED and for patients ≥80 years, the time threshold was reduced to 4.2, 5, 5, and 5.1 min, respectively.

Figure 1 shows the adjusted ORs for survival to hospital discharge of OHCA when the response time cut-off values were set as 5.2 min, 6.2 min, and 7.2 min. The adjusted ORs of per minute shorter response times were 1.217 (95% CI: 1.140–1.299, $p < 0.001$). For response time less than 5.2, 6.2, and 7.2 min, the ORs were 1.832 (95% CI: 1.375–2.440,

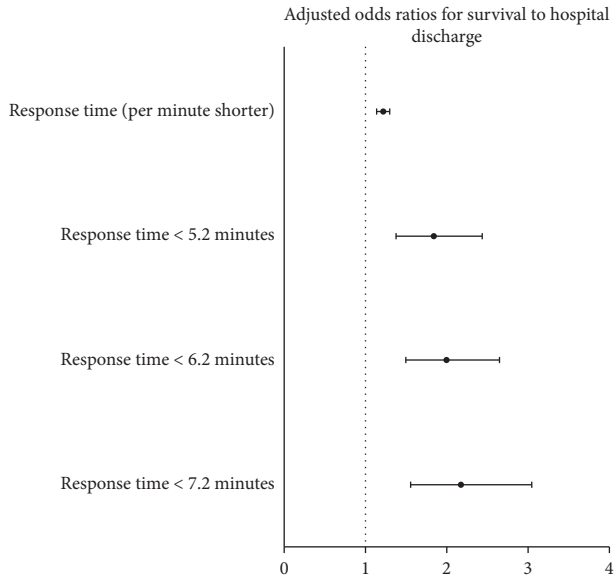

Figure 1: OR and 95% CI for survival to hospital discharge in OHCA patients after adjusting for age, witness presence, public location, bystander CPR, EMT-P attendance, and prehospital defibrillation by AED.

$p < 0.001$), 1.992 (95% CI: 1.496–2.653), and 2.175 (95% CI: 1.553–3.047), respectively.

4. Discussion

In this study, we estimated the EMS response time threshold under different conditions. We found that a short EMS response time was associated with a high rate of survival to hospital discharge after OHCA. The optimal response time threshold for survival to hospital discharge was 6.2 min. In the case of OHCA in public areas or with bystander CPR, the threshold was prolonged to 7.2 min and 6.3 min, respectively; and in the absence of a witness, the threshold was shortened to 4.2 min. Previous studies have focused on the EMS response time threshold for OHCA. Ono et al. collected data from 2,04,277 episodes of bystander-witnessed OHCA and found that the threshold for favorable neurological outcome in OHCA patients was 6.5 min, and the threshold could be prolonged from 1 min to 7.5 min with bystander CPR [7]. Lee et al. demonstrated that the response time thresholds for return of spontaneous circulation (ROSC), survival to discharge, and favorable neurologic outcomes were 11.5, 7.5, and 7.5 min [16]. In the current study, the response time threshold for survival to hospital discharge was 6.2 min. The threshold was shorter in the current study than those reported in previous studies by Ono et al. and Lee et al. One possible explanation for this is the difference in the patient characteristics. Ono et al. only included patients with witnessed OHCA; Lee et al. only included OHCA patients with presumed cardiac etiology by emergency physicians in the ED. We included OHCA patients with or without a witness and with various comorbidities. In our study, the response time threshold for OHCA with a witness was 6.2 min, and the threshold in the study of Ono et al. was 6.5 min. Another possible explanation for the difference is the variation in prehospital management in Taiwan and Japan. In Japan, the ambulance usually has at least one emergency life-saving technician on board, who is allowed to insert an intravenous line. Some of them who are specially trained are allowed to insert tracheal tubes and administer intravenous epinephrine [17]. In Taiwan, EMS agents can be classified as EMT-I, EMT-II, and EMT-P. The differences between EMT-I, EMT-II, and EMT-P lie mainly in the type and duration of the training program and what they are authorized to do. The total training program time to qualify for EMT-I, EMT-II, and EMT-P roles was 40 h, 280 h, and 1280 h, respectively. All EMS agents can perform BLS, LMA insertion, and defibrillation, but only EMT-P agents are authorized to perform advanced life support (ALS) procedures, including intubation, insertion of intravenous lines, and administration of certain medications, such as epinephrine and amiodarone [2]. Ono et al. reported that 29.8% to 33.6% of OHCA patients received an intravenous line; in our study, only 27.0% of the OHCA patients were treated by an EMT-P. This difference might impact the outcome and EMS response time threshold. In fact, the threshold for the group attended by EMT-P (6.2 min) was longer than the threshold for the group attended by other EMTs (5 min). In 2018, the National Development Council of Taiwan set the target response time to 6 min, and the target achievement rate was 90% (https://english.ey.gov.tw/). Mathiesen et al. found that rural regions are associated with prolonged response time and poor outcome [3]; Ho et al. also showed that OHCA occurring at night is associated with prolonged response time [4]. Our results suggest that bystander CPR might extend the threshold of survival to hospital discharge in OHCA patients. Hence, bystander CPR education and earlier recognition of OHCA might help to improve the outcomes of OHCA.

Bystander CPR was found to be associated with survival to hospital discharge and favorable neurological outcomes for OHCA patients [8, 13, 18]. Bystander CPR is associated with a prolonged EMS response time threshold [7]. In our study, bystander CPR prolonged the response time threshold by 0.2 min (6.1 to 6.3 min), but in the study by Ono et al., it prolonged the threshold by 1 min. This variation might be due to the quality of CPR provided by the bystander and the time window between cardiac arrest and CPR initiation. Axelsson et al. collected OHCA data over a 20-year period in Sweden and concluded that OHCA witnessed by an EMS agent had a better prognosis than OHCA not witnessed by an EMS agent [19]. One reason for the good prognosis was the short time window between the collapse and the start of CPR. Sasson et al. reviewed 79 studies and found that 53% (95% CI, 45.0–59.9) of cardiac arrest patients were witnessed by a bystander, and only 32% (95% CI, 26.7–37.8) received bystander CPR [20]. There might be a delay between the collapse and provision of bystander CPR. However, the time window from the onset of cardiac arrest to the start of CPR was not recorded in the present study, and the quality of bystander CPR was difficult to evaluate. Increased awareness of patients and their family members might help them to recognize the warning symptoms of OHCA and initiate

timely CPR [19]. In contrast, dispatcher-assisted telephone CPR might shorten the delay time from collapse to CPR initiation, and thus, it is associated with a higher survival rate and better neurological outcomes [21, 22]. In Kaohsiung, the Fire Bureau of Kaohsiung City Government also tried to promote dispatcher-assisted telephone CPR, and the execution rate has also increased in recent years (https://fdkc.kcg.gov.tw/en/). However, some problems exist in telephone CPR, such as incorrect medical condition reporting and quality of CPR performed [23, 24]. Further efforts might focus on dispatcher-assisted telephone CPR, warning symptoms of OHCA recognition, and CPR education.

Many previous studies have shown prehospital factors, such as location of OHCA [3, 25], presence of a witness [20], EMT-P response [2, 26], bystander CPR [18, 27], and prehospital AED use [9, 18, 27]. In the present study, we found that the presence of a witness, public location, bystander CPR, EMT-P response, and defibrillation by AED were independently associated with survival to hospital discharge. Luc et al. examined 6,918 OHCA cases and found that the 30-day survival rate increased from 4.9% to 10.4% when the OHCA event was witnessed and immediate CPR was initiated [27]. Recently, Kern et al. designed a simulation study and found that neighborhood volunteer networks might improve response time [28]. However, there is still no evidence to effectively shorten the time interval from cardiac arrest to CPR initiation in the real world.

Comorbidities can be considered prognostic factors for OHCA, but this point remains controversial. Andrew et al. collected data of 15,953 OHCA patients and found that a high Charlson Comorbidity Index (CCI) was independently associated with low odds of survival to hospital discharge, 1-year functional recovery, and favorable 1-year health-related quality of life [14]. Hirlekar et al. also found that renal disease, diabetes, metastatic carcinoma, and congestive heart failure were independently related to 30-day survival rate [10]. On the other hand, Lai et al. showed that cardiac comorbidities, such as cardiomyopathy and valvular heart disease, were predictors of improved survival in cardiac arrest patients [11]. A review article on 29 observational studies concluded that comorbidities were negatively associated with outcomes in most reported results [29]. Our study did not find a statistically significant difference in comorbidities between the "survival to hospital discharge" and "mortality" groups. One possible reason is that only specific comorbidities were recorded in our study. The lack of a comprehensive view of prearrest comorbidities, such as the CCI, might have influenced the results of this study. Second, prehospital factors, conditions during resuscitation, and post-resuscitation care might counter the impact of prearrest comorbidities. In our study, prehospital factors, such as EMS response time, witnessed OHCA, public location, bystander CPR, EMT-P response, and prehospital defibrillation by AED, may have played a more important role in the prognosis of OHCA than pre-existing morbidities.

There are some limitations to the present study. First, this was a retrospective observational study. Second, the database was restricted to only one city with a single-tiered EMS system, and the results might be different for other cities with different EMS systems. Third, we might have missed OHCA patients who failed to call the EMS and were sent to the hospital by family or health care units. Fourth, our study did not assess the quality of bystander CPR, time of bystander CPR initiation, resuscitation drugs (such as epinephrine, treatment during hospitalization), or dispatcher-assisted CPR.

5. Conclusions

We found that a short EMS response time was associated with a high rate of survival to hospital discharge after OHCA. The optimal response time threshold for survival to hospital discharge was 6.2 min. In the case of OHCA in public areas or with bystander CPR, the threshold was prolonged to 7.2 min and 6.3 min, respectively; and in the absence of a witness, the threshold was shortened to 4.2 min.

Data Availability

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Research Article

Impact of Application of Multifunction Electrode (MFE) Pads on Cardiopulmonary Resuscitation Quality

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Background. Early defibrillation and high-quality chest compressions are crucial in treatment of sudden cardiac arrest (SCA) subjects. The aim of this study was to assess an impact of defibrillation methods on cardiopulmonary resuscitation (CPR) quality. *Methods*. A randomized simulation cross-study was designed, in which 100 two-person paramedical teams participated. Two 10-minute scenarios of SCA in the mechanism of ventricular fibrillation were analysed. In the first one, teams had at their disposal defibrillator with hard paddles (group C), whereas in the second one, adhesive electrodes were used (group MFE). The CPR quality was evaluated on the basis of the chest compression parameters (rate, depth, recoil, compression fraction (CCF), and no-flow time), airways patency achievement, and successful emergency drug administration. *Results*. Substituting standard hard paddles with adhesive electrodes led to an increase in CCF (77% vs 73%; $p < 0.05$), higher rate of complete chest recoil, and a decrease in no-flow time (6.0 ± 1.1 vs. 7.3 ± 1.1; $p < 0.001$). The airway patency was ensured sooner in group MFE (271 ± 118 s vs. 322 ± 106 s in group C; $p < 0.001$). All teams in scenario with adhesive electrodes were able to administer two doses of adrenaline, meanwhile only 74% of them in group C ($p < 0.001$). Moreover, in 8% of group C scenarios, paramedics did not have enough time to administer amiodarone. *Conclusion*. Our simulation-based analysis revealed that use of adhesive electrodes during defibrillation instead of standard hard paddles may improve the quality of CPR performed by two-person emergency team.

1. Introduction

Sudden cardiac arrest (SCA) in prehospital settings affects an increasing number of patients. Only in the United States of America, 420,000 OHCA cases are reported annually [1]. The latest data collected in 27 European countries by in EuReCa ONE registry showed the prevalence of out-of-hospital cardiac arrest (OHCA) ranged from 19.0 to 104.0 cases per 100,000 [2].

All scientific societies of medical specialists in emergency medicine agree that SCA requires active and proper interventions to restore circulation [3, 4]. It is a general consensus that if defibrillation procedure is implemented faster, spontaneous circulation is more likely to return. The guidelines of the European Resuscitation Council emphasize that every minute of defibrillation delay reduces the chance of OHCA survival by 10–12%. However, the rapid implementation of defibrillation can increase survival by up to 50–70% [3, 4]. Public defibrillation programs are being developed in many countries. In Japan, survival of OHCA with favourable neurological results has increased significantly due to AED accessible in public places [5].

Another aspect of resuscitation is a permanent shortage of public funds to cover all requirements of national healthcare system resulted, among many others, and in reduction in number of paramedics in the emergency medical teams. In many developed countries, a standard consists of a two-person team well-equipped with sophisticated and novel devices, including defibrillators compliant with adhesive electrodes.

The aim of our analysis was to assess the impact of two types of defibrillation methods, namely, standard hard paddles and adhesive electrodes, on the quality of cardiopulmonary resuscitation.

2. Materials and Methods

2.1. Study Design and Participants. A randomized simulation cross-study was designed, in which 100 two-person teams of paramedics participated. They were randomly selected from a group of 300 professionally active paramedics with a minimum of five-year experience. The age of the study participants ranged from 27 to 55 years. All paramedics took part in the study voluntarily. The study protocol was approved by the local bioethical committee (No. KB 1075/19). The research project did not have any source of funding. The randomization procedure was prepared with a use of a free online randomization tool (http://www.randomizer.org). The allocation to the first group was randomized.

2.2. Study Protocol. Each team participated in two 10-minute simulated scenarios of SCA with the persistent ventricular fibrillation rhythm. In the first one, teams used defibrillator with hard paddles (group C), whereas in the second one, paramedics had only adhesive electrodes at their disposal (group MFE). To standardize the operation of all teams, they were forced to use the same method of defibrillation—a model that involves charging the defibrillator just before performing the analysis. Paramedics participating in the study received information that all activities were to be carried out in real time. The teams had 15-minute breaks between the scenarios. All simulations were supervised by qualified medical simulation instructors.

2.3. Simulator. In our study, high-fidelity simulator (Resusci Anne QCPR, Laerdal Medical, Stavanger, Norway) was used. This dummy registered chest compression parameters. Moreover, effects of the other medical emergency procedures such as intubation, mechanical ventilation, and defibrillation were visible on this dummy. Its hands were filled with blood, so paramedics could see whether intravenous angiocatheters were inserted correctly.

2.4. Equipment and Medicines. Before starting the scenario, each team was thoroughly acquainted with the available equipment and work environment. A standard defibrillator (M-Series, ZOLL, Chelmsford, USA) was equipped with manual paddles or adhesive electrodes. The electrodes for each use were originally packed. Before commencing the scenario, the device was thoroughly discussed, and team members could practice on it. Paramedics were equipped with a medical bag that contained necessary medications, liquids, needles, catheters, syringes, devices for clearing the respiratory tract, patches, and boxes for sharp objects. This equipment could be arranged individually in a bag by each team.

2.5. Assessed Parameters of CPR. Available parameters of chest compressions quality were recorded by means of the Laerdal PC Skill Reporting System program version 2.0 (Laerdal Medical, Stavanger, Norway). The following parameters such as CCF, average no-flow time, correct hand placement, total number of compressions, average depth of compressions, percentage of appropriately deep compressions, percentage of compressions with adequate chest relaxation (chest recoil), the average compressions rate, and the percentage of the correct compressions rate were recorded. Additionally, the duration of defibrillation itself was measured in both groups.

Moreover, we evaluated time to assure airways patency (i.e., successful introduction of supraglottic airways device (SAD)) and to administer the consecutive doses of drugs commonly injected during CPR such as amiodarone and adrenaline.

2.6. Data Management and Statistical Analysis. The data recorded by the reporting PCI system incorporated in simulator were entered into a previously prepared Excel spreadsheet. Regarding continuous data, they were checked for normality with the use of the Shapiro–Wilk W test. Those satisfying the criteria of normal distribution were expressed as the mean with standard deviation (sd), and paired Student's t-test was applied to estimate differences between groups. Continuous data that cannot be assumed to be normally distributed were presented as the medians (25th and 75th percentiles) and then analysed by means of the Wilcoxon matched-pairs test. The categorical variables were expressed as the numbers (n) with percentage (%), and then, they were compared between subgroups with the use of the Yates corrected χ^2 test. A p value below 0.05 was considered of statistical significance. The statistical analysis was performed with the use of Statistica 10.0 for Windows (StatSoft, Inc., Tulsa, OK, USA).

3. Results

Replacing standard defibrillation paddles (group C) with MFE Pads led to an improvement in chest compression quality estimated on the base of CCF, no-flow time, and parameters of compressions themselves such as optimal rate, depth, and recoil after every compression. CCF was significantly higher in group MFE, while no-flow time was lower compared to group C. Detailed results of statistical analysis regarding chest compression adherence to the recommendations are outlined in Table 1.

Table 1: Selected parameters of chest compression in both groups.

CC parameters*	Group MFE ($n = 100$)	Group C ($n = 100$)	p value
CC rate (minute)	121 ± 9	122 ± 8	0.691
Correct CC rate (%)	36 (16; 59)	33 (12; 47)	0.064
CC depth (mm)	55 ± 5	52 ± 4	<0.001#
Correct CC depth (%)	53 (45; 60)	45 (32; 55)	<0.001#
Correct chest recoil (%)	32 (22; 48)	19 (9; 38)	0.001#
Correct hands position (%)	100 (99; 100)	100 (98; 100)	0.372
CCF (%)	77.0 ± 6.5	73.1 ± 7.1	<0.001#
No-flow time (sec)	6.0 ± 1.1	7.3 ± 1.1	<0.001#

*Continuous variables are expressed as means with standard deviations (with normal distribution) or medians (25th; 75th percentile). #Statistically significant differences between studied groups ($p < 0.05$). C = control; CC = chest compression; CCF = chest compression fraction; MFE = multifunction electrode.

3.1. Defibrillation. In all cases of group MFE, defibrillation was performed five times within 10-minute scenarios, whereas 86% in group C cases ($p = 0.001$). Moreover, all except one application was faster in group MFE than in C. The detailed data are presented in Table 2.

3.2. Different Methods of Defibrillation and Airway Patency. In the group MFE, SAD insertion manoeuvres were initiated significantly ($p < 0.05$) earlier after CPR initiation (213 ± 112 s) and lasted shorter (57 ± 27 s) than in group C (243 ± 100 s and 79 ± 39 s, respectively). Consequently, airway patency was assured faster in the earlier group (271 ± 118 s vs. 322 ± 106 s) ($p < 0.001$).

3.3. Impact of MFE Pads on Drug Administration. Paramedics injected two doses of adrenaline in all scenarios with MFE pads, whereas, in group C, 74% ($p < 0.001$). Similarly, significant differences were noted regarding administration of amiodarone. Of note, in 8% of scenarios in group C, no single doses of amiodarone, although prepared, were used (Figure 1). It could have resulted from later obtaining venous access in the latter group (Figure 2). It should be stressed that the action of peripheral venous access insertion was started only slightly later but lasted longer in group C than group MFE.

Table 2: Time of consecutive applications of defibrillations.

No.*	Group MFE	Group C	p value
1st defibrillation	39.0 ± 10.6 (100)**	50.4 ± 16.8 (100)	<0.001
2nd defibrillation	166.6 ± 23.0 (100)	179.8 ± 28.1 (100)	0.011
3rd defibrillation	290.2 ± 24.0 (100)	313.1 ± 39.6 (100)	0.001
4th defibrillation	413.3 ± 25.1 (100)	440.9 ± 49.1 (100)	0.001
5th defibrillation	535.9 ± 24.5 (100)	535.1 ± 63.0 (86)	0.785

**Data are expressed as mean with standard deviation (sd); *number of analysed defibrillations. C = control; MFE = multifunction electrode.

4. Discussion

It is commonly accepted and supported by valid guidelines that high-quality chest compressions and early defibrillation have the greatest impact on SCA survival. Both actions should be implemented as soon as possible [6]. Their initiation and optimal continuation may be a real challenge if the must be performed by only two-person emergency teams. Thus, application of some devices reducing involvement of both paramedics may be very helpful. In this study, importance of adhesive electrodes compliant with standard defibrillator on CPR quality has been tested. Having in mind that CPR confines many single actions performed by paramedics, many of them such as chest compressions, defibrillation, airways patency, access to peripheral vein, and emergency drugs administration were included in our analysis.

Strictly defined parameters of high quality of chest compressions are associated with optimal frequency of return of spontaneous circulation (ROSC) and survival rate. The frequency should be kept between 100 and 120 compressions per minute while the depth 5 through 6 cm. The reverse association between rate and depth was noted before [7, 8]. Moreover, the experimental studies in animal models revealed the importance of chest wall recoil. This causes negative chest pressure formation which facilitates venous return to the heart. By generating the phenomenon described above, it is possible to increase coronary perfusion pressure [9]. It was found in our study that although chest compressions performed by experienced paramedics in simulated scenarios were far from optimal, application of self-adhesive electrodes in the MFE group was linked to marked improvement in correct compression depth and chest recoil. The guidelines also emphasize a significant value of minimizing breaks during chest compressions. The American Heart Association experts have established a parameter called CCF (chest compression fraction) defined as the percentage of time spent on uninterrupted chest compressions. The optimal CCF value should be at least 80% [10]. This value is also confirmed by clinical experience, which shows that the best prehospital cardiac arrest survival results are achieved while maintaining CCF values within 81–100% [11]. Our study showed an increase in the CCF and corresponding decrease in no-flow time in group MFE. It must be stressed that, even in the latter subset, average value of 77% was too low to ensure optimal chest compression quality. A significant improvement regarding these aforementioned parameters may result from no need of placing standard ECG electrodes on a chest to proceed with analysis and consecutive defibrillation.

Previous studies showed that the highest survival rate was recorded among patients with diagnosed VF/pVT when chest compressions were initiated and defibrillation was

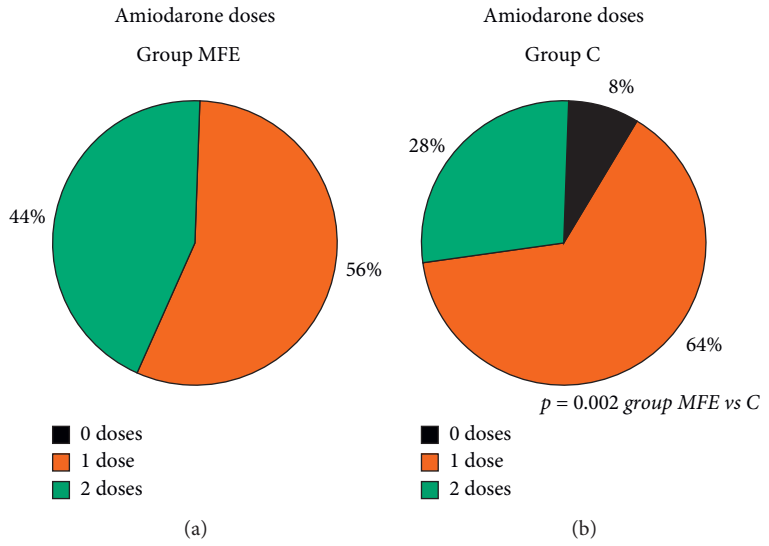
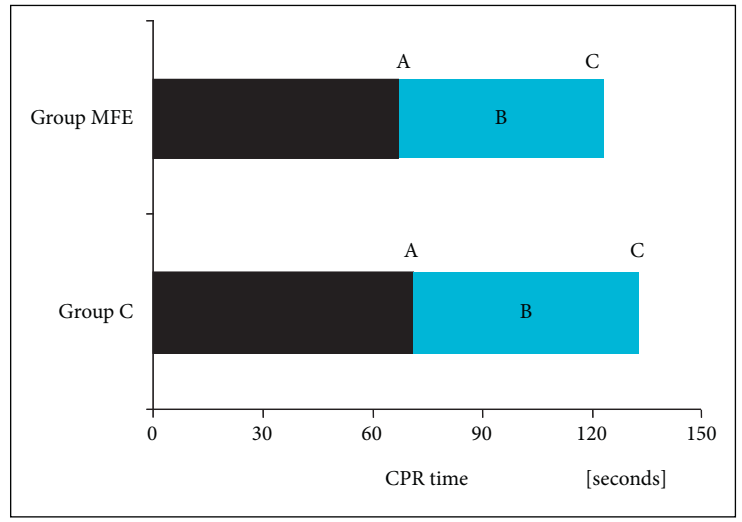


Figure 1: Number of amiodarone injections in both groups.



A = initiation of action; B = duration of obtaining venous access; C = completion of action

*[s]	A	B	C
Group MFE	67 (50; 86)	56 (43; 69)	125 (111; 155)
Group C	71 (58; 95)	70 (49; 90)	140 (128; 166)
P value	0.133	0.027	0.016

*All values are expressed as median (25th; 75th percentile)

Figure 2: Obtaining of peripheral venous access in the studied groups.

carried out within the first 3–5 minutes following the loss of consciousness [12]. In case of unavailability of defibrillator at the site of OHCA, mechanical resuscitation before professional medical intervention increases survival rate of SCA subjects. Our study showed that all defibrillations were performed earlier in group MFE. Exception was the fifth defibrillation, but it must be stated that, in group C, it was performed in 86% of scenarios while, in 100%, in group MFE.

Up to now, three main models of defibrillator charging and chest compression have been developed [13]. In the first one, chest compressions are stopped to analyse heart rhythm, charge the defibrillator, and eventually defibrillation. After the latter, one compression is resumed. The pauses in chest compression are the longest. In the second one, compressions are suspended just for heart rhythm analysis and defibrillation itself. During charging of defibrillation, taking place after rhythm analysis, the chest is compressed. In the last model, charging of defibrillator is done blindly even before rhythm analysis. It was shown that irrespective of the described above model, the breaks in chest compressions depended on a form of defibrillation devices.

If paddles are employed, key compression and defibrillation times will depend on place of charging, i.e., on the device or on the patient's chest. If self-adhesive defibrillation pads are used for defibrillation, charging can be performed blindly before or after the rhythm analysis [13, 14]. Additionally, their application can significantly reduce the delay in performing the defibrillation [14]. Our analysis confirmed this finding. This is probably the main mechanism underlying the clinical observation that self-adhesive pads during cardiopulmonary resuscitation increase the frequency of ROSC and in-hospital survival. More advantages of these electrodes have been advocated. They are invaluable for carrying out cardioversion or percutaneous stimulation in cardiac surgical patients during and soon after invasive open-chest procedures [15].

Patients with OHCA whose proper heart rate was restored require to be transported to hospital as soon as possible. They are at high risk of cardiac arrest or other cardiac arrhythmias. Application in them of self-adhesive pads for transport is extremely important as defibrillation can be delivered immediately, or transdermal stimulation can be initiated without any delay [16] The use of self-adhesive pads can significantly facilitate other necessary procedures carried out by paramedics during CPR, particularly in challenging prehospital conditions characterized by the pressure of a large number of distractions such as bystanders present near the patient, noise at the place of incident, fatigue, poor nutrition, or lack of sleep. The human factor in this work is extremely important, and simplification of procedures allows paramedics to focus on the priorities of action [17]. We found in our study that self-adhesive electrodes had also positive impact of other procedures. Paramedics in MFE scenario decided faster about SAD application, and airways patency was achieved faster in this subset. The access to peripheral vein went smoother in group MFE; the majority of study participants were able to complete the algorithm of emergency drugs administration, whereas it was not possible in many scenarios in the control group. Teams using standard paddles did not have enough time to inject the second dose of amiodarone.

The results of the aforementioned studies were reflected in the current guidelines, both AHA and ERC that recommended the use of self-adhesive pads. This is argued by the numerous benefits of defibrillation using paddles [18, 19]. On the other side, the self-adhesive pads have also potential disadvantages. If they are attached to the anterior aspect of the chest wall, they can interfere with radiographic visualization of the heart. To overcome this problem, the pads of different shapes have been designed [20]. Monitoring of heart rate with the use of them, which was previously used for defibrillation, showed that, during the discharge, the electrolyte gel gets polarized. This process creates a risk that a false asystole may appear on the ECG monitor. The authors of this study recommend the use of monitoring cable to confirm the actual heart rhythm [21].

At last, costs of their routine use are a huge financial problem. Pinkham-Reidy et al. on the basis of cost-effectiveness analysis showed that routine use of these pads resulted in high costs for the healthcare system and should be applied only if indicated [22].

5. Conclusion

Our simulation-based analysis revealed that use of adhesive electrodes during defibrillation instead of standard hard paddles may improve the quality of cardiopulmonary resuscitation performed by two-person emergency team.

Data Availability

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

Disclosure

The authors alone are responsible for the content and writing of this paper.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Research Article

Occurrence and Impact of Gastrointestinal Bleeding and Major Adverse Cardiovascular Events during Sepsis: A 15-Year Observational Study

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Objective. Sepsis patients are at risk of gastrointestinal bleeding (GIB) and major adverse cardiovascular events (MACEs), but few data are available on the occurrence of GIB and MACEs and their impact on sepsis outcomes. *Methods*. The medical claims records of 220,082 patients admitted for sepsis between 1999 and 2013 were retrieved from the nationwide database. The adjusted odds ratios (aORs) of composite outcomes including the hospital mortality, intensive care unit (ICU) admission, and mechanical ventilation (MV) in patients with a MACE or GIB were estimated by multivariate logistic regression and joint effect analyses. *Results*. The enrollees were 70.15 ± 15.17 years of age with a hospital mortality rate of 38.91%. GIB developed in 3.80% of the patients; MACEs included ischemic stroke in 1.54%, intracranial hemorrhage (ICH) in 0.92%, and acute myocardial infarction (AMI) in 1.59%. Both ICH and AMI significantly increased the risk of (1) ICU admission (aOR = 8.02, 95% confidence interval (CI): 6.84–9.42 for ICH and aOR = 4.78, 95% CI: 4.21–5.42 for AMI, respectively), (2) receiving MV (aOR = 3.92, 95% CI: 3.52–4.40 and aOR = 1.99, 95% CI: 1.84–2.16, respectively), and (3) the hospital mortality (aOR = 1.08, 95% CI: 0.98–1.19 and aOR = 1.11, 95% CI: 1.03–1.19, respectively). However, sepsis with GIB or ischemic stroke increased only the risk of ICU admission and MV but not the hospital mortality (aOR = 0.98, 95% CI: 0.93–1.03 for GIB and aOR = 0.84, 95% CI: 0.78–0.91 for ischemic stroke, respectively). *Conclusions*. GIB and MACEs significantly increased the risk of ICU admission and receiving MV but not the hospital mortality, which was independently associated with both AMI and ICH. Early prevention can at least reduce the complexity of clinical course and even the hospital mortality.

1. Introduction

Sepsis is a complex syndrome induced by severe infection and involving acute organ failure [1]. Despite advances in drugs and treatment modalities, management of sepsis patients is a critical care challenge [2, 3]. Decreasing the occurrence of sepsis-associated complications would be expected to improve hospital mortality and the clinical course by reducing the need for intensive care unit (ICU) admission and mechanical ventilation (MV) support. Few data on the incidence and impact of major adverse cardiovascular events (MACE) and gastrointestinal bleeding (GIB) in sepsis patients are available even though the concurrent development of MACE and GIB in sepsis patients is not unusual [4].

An analysis of over 119,000 patients hospitalized with sepsis between 2003 and 2012 and included in a nationwide database in the USA estimated that the incidence of GIB was

5.4% (6,571/119,684 patients). Concurrent GIB was found to increase sepsis mortality by 9% [5]. Sepsis-associated atrial fibrillation, coagulopathy, hemodynamic instability, and prolonged systemic inflammation act to trigger acute ischemic stroke. Ischemic stroke events are not unusual in patients with sepsis and thrombocytopenia, but the cause appears to be complex [6–9].

An analysis of data from over 2.6 million sepsis patients included in a national inpatient database in the USA from 2002 to 2011, found that 4.5% (118,183/2,602,854 patients) had a concurrent, nonprimary diagnosis of AMI during hospitalization. Non-ST-elevation AMI was the diagnosis of 71.4% of those cases. Hospital mortality was higher in sepsis patients with AMI (35.8%) than those with sepsis alone (16.8%, $P < 0.001$; adjusted odds ratio (aOR) = 1.24, 95% confidence interval (95% CI): 1.22–1.26). Invasive management concurrent AMI was associated with reduced mortality compared with conservative management (OR 0.47, 95% CI: 0.44–0.50) [10].

The treatment of sepsis patients with concurrent GIB and a MACE is complicated by difficulties in choosing among antiplatelet, anticoagulation, and hemostasis drugs. The use of predisposing medications such as antiplatelet drugs, anticoagulants, and proton pump inhibitors (PPIs) before or during the course of sepsis also complicates treatment.

This study used the 15-year nationwide database of Taiwan that included data from 1999 to 2013. The data were from 220,082 patients who were first admitted for sepsis to determine the frequency of occurrence of GIB and MACEs in the course of sepsis. The impacts and interactions of MACE and GIB on the composite outcomes of the hospital mortality, ICU admission, and receiving MV were analyzed.

2. Methods

2.1. Data Source. The study database included anonymized patient and claims information retrieved from the National Health Insurance Research Database (NHIRD) of Taiwan. The records of 220,082 inpatients who were first admitted with a diagnosis of sepsis between 1999 and 2013 were included in the analysis. The NHIRD is maintained by the National Health Insurance Program, which was launched by the National Health Insurance Administration (NHIA) in 1995, and currently provides coverage for more than 23.03 million residents (>99% of the entire population). The NHIRD included the data from the clinic, district hospital, regional hospital, and medical center. The confidentiality and quality of the NHIRD data have been documented in previous studies [11–14].

2.2. Study Participants. Sepsis patients were identified by ICD-9-CM discharge diagnosis code 038 from the NHIRD. The positive predictive value of the sepsis (92.3%) and septic shock (97.0%) diagnoses have been previously validated [12, 15].

All the enrolled sepsis patients should include a main diagnosis coding of sepsis in the first or second diagnostic coding plus a coding representing the infection origin within the first three diagnoses. The infection origin coding was referred to Angus et al. in 2001 [16]. Besides, GIB or MACE could not be the first diagnosis code or have been entered before a diagnosis code for sepsis [17, 18].

2.3. MACEs and GIB. The MACEs were defined by referring to International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM), as the compositions of acute myocardial infarction (AMI) (ICD-9-CM 410), ischemic stroke (ICD-CM-9: 433,434.1, 434.9, and 435) and intracranial hemorrhage (ICH) (ICD-9-CM: 430.xx, 431.xx, 767.0, and 772.2). GIB was defined by ICD-CM-9: 578.9.

2.4. Potential Confounders. We systematically identified the potential confounders in the claims data. The identified confounding factors were age, sex, insurance premium (as a proxy of household income), level of urbanization, baseline comorbidities, and medications. The baseline comorbidities were (1) hypertension (HTN) (ICD-9-CM: 401–405), (2) diabetes mellitus (DM) (ICD-9-CM: 250, 357.2, 362.01, 362.02, and 366.41), (3) congestive heart failure (CHF) (ICD-9-CM: 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, and 428.0), (4) chronic obstructive pulmonary disease (COPD) (ICD-9-CM: 490, 491, 492, 494, and 496), (5) chronic liver disease (CLD) (ICD-9-CM: 571), (6) chronic kidney disease (CKD) (ICD-9-CM: 581–588, 403–404, 285.21, and 250.4), and (7) cancer (ICD-9-CM: 140–208). Drug use was identified by claims indicating use for more than 1 week within a one-year period prior to the index date.

2.5. Selection Process. Patients <18 or >100 years of age or infected with human immunodeficiency virus were excluded from the study. In the patients with repeated admissions, only data from the first hospitalization for sepsis between 1999 and 2013 were included in the analysis. The date of admission for the first hospitalization for sepsis was defined as the index date. Comorbidities were identified by ICD-9-CM codes of diagnoses made within a one-year period prior to the index date.

2.6. Ethical Approval. As the database contained deidentified data for research, the study was exempted from obtaining informed consent from the participants. This study was approved by the Institutional Review Board of Taichung Veterans General Hospital (CE18102A) and China Medical University (CMUH104-REC2-115).

2.7. Statistical Analysis. Differences in demographic characteristics, baseline comorbidities, drug use (including aspirin, clopidogrel, warfarin, metformin, nonsteroidal anti-inflammatory drugs, statins, PPIs, steroids, and immunosuppressants), and the composite outcomes (total hospital mortality, ICU admission, and MV) were compared by the chi-squared or two-sample t-test.

Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for each variable in the logistic regression model. Adjusted ORs (aORs) for total hospital mortality, ICU admission, and receiving MV were obtained after adjusting for potential confounders including age, sex, insurance premium (a proxy for household income), urbanization level (a proxy for the accessibility of medical care), and comorbidities [15]. The Kaplan–Meier analysis was conducted to compare the cumulative incidence of hospital mortality between the patients with and without GIB and MACE, respectively.

Joint effect analysis was used to analyze the synergistic impact of sepsis complications including GIB, ischemic stroke, ICH, and AMI, on total hospital mortality, ICU admission, and MV. The 16 possible combinations of the four complications were evaluated using uncomplicated sepsis as the reference. The aORs of each combination of complications were calculated by logistic regression after adjusting for age, sex, insurance premium, urbanization level, and baseline comorbidities.

The statistical analysis was performed with SAS 9.4 (SAS Institute, Inc., Cary, NC, USA). P values ≤ 0.05 were considered significant.

3. Results

3.1. Demographic Characteristics, Baseline Comorbidities, and Clinical Presentation. After exclusion, a total of 220,082 patients with a first admission for sepsis between 1999 and 2013 were retrieved from the nationwide database. The patient characteristics are shown in Table 1. The mean age was 70.15 ± 15.17 years and 56.39% was men. Hypertension was the most common comorbidity (68.31%), followed by diabetes mellitus (DM, 62.19%) and chronic obstructive pulmonary disease (45.64%). The most frequent medications were PPIs (41.73%), aspirin (13.11%), and clopidogrel (8.03%). Septic shock developed in 50.78% of the patients (111,754/220,082), and total hospital mortality was 38.91% (85,638/220,082). The clinical course of sepsis was accompanied by GIB in 3.80%, ischemic stroke in 1.54%, ICH in 0.92%, and AMI in 1.59% of cases. The origins of sepsis were primarily respiratory system (39.87%), genitourinary (30.22%), and gastrointestinal/biliary-tract (8.09%) infections.

3.2. Logistic Regression Analysis of Total Hospital Mortality, ICU Admission, MV, and Complications of Sepsis. After adjusting for age, sex, insurance premium, urbanization level, and baseline comorbidities, the aOR of GIB for total hospital mortality was 0.98 (95% CI, 0.93–1.03), the aOR for ICU admission was 1.30 (95% CI, 1.23–1.38), and the aOR for MV was 1.32 (95% CI, 1.26–1.40) with uncomplicated sepsis as the reference (Table 2). Ischemic stroke was associated with an increased risk of ICU admission (aOR = 2.71, 95% CI, 2.47–2.97) and MV (aOR = 2.07, 95% CI, 1.90–2.25) but did not affect the risk of hospital mortality (aOR = 0.84, 95% CI, 0.78–0.91). ICH and AMI had similar effects on sepsis outcomes. In complicated sepsis, ICH increased the risk of total hospital mortality (aOR = 1.08, 95% CI, 0.98–1.19), ICU admission (aOR = 8.02, 95% CI, 6.84–9.42), and MV (aOR = 3.92, 95% CI, 3.52–4.40) compared with uncomplicated sepsis. The corresponding aORs for AMI were 1.11 (95% CI, 1.03–1.19) for total hospital mortality, 4.78 (95% CI, 4.21–5.42) for ICU admission, and 1.99 (95% CI, 1.84–2.16) for MV.

3.3. Kaplan–Meier Analysis with the Log-Rank Test. In the Kaplan–Meier analysis, the patients with sepsis complicated with AMI and ICH had a higher cumulative incidence of hospital mortality than those without AMI or ICH (log-rank test, $P < 0.001$) (Figures 1 and 2). However, the opposite phenomenon was observed in patients with ischemic stroke and GIB (log-rank test, $P < 0.001$) (Figures 3 and 4).

3.4. Joint Effect Analysis of GIB and MACE on Hospital Mortality, ICU Admission, and MV. The results of joint effect analysis shown in Table 3 summarize the sepsis outcomes if two or more complications occurred at the same time. The patients may have needed contrasting treatment during the sepsis course. For example, GIB needs hemostasis and cessation of antiplatelet drugs, and ischemic stroke needs antiplatelet drugs. GIB plus any MACE complicated the sepsis course by increasing ICU admissions and receiving MV. The combination did not affect total hospital mortality. Similar results were observed for other combinations such as AMI plus ischemic stroke. No specific combination of thrombotic complications such as ischemic stroke and AMI or hemorrhagic complications, such as GIB and ICH, significantly increased the risk of hospital mortality. However, the occurrence of more than one complication changed the clinical course, for example, by increasing the risk of ICU admission and MV. The combination of three or four complications was omitted because there were very few cases.

4. Discussion

To the best of our knowledge, this is the first and largest cohort study to comprehensively describe the individual and combined impact of GIB and MACE complications of sepsis in patients with a primary diagnosis of sepsis at the time of admission. Analysis of nationwide claims data in a cohort of sepsis patients found that GIB and MACE were associated with significantly increased risks of ICU admission and receiving MV for critical care and treatment of respiratory failure. Except for AMI and ICH, the complications did not affect mortality. In conclusion, GIB and MACE may not have a serious effect on hospital mortality as serious as was previously thought, and their occurrence will undoubtedly increase the complexity of the sepsis and hospital course. The use of preventive medications such as antiplatelet drugs, anticoagulants, statins, and PPIs should be monitored and balanced throughout the sepsis course.

Table 1: Demographic characteristics and baseline comorbidities of sepsis patients.

Variables ($n = 220,082$)	Total		Hospital mortality				P value
			No		Yes		
	n	%	n	%	n	%	
Sex							<0.001
Female	95,982	43.61	62,472	46.47	33,510	39.13	
Male	12,4100	56.39	71,972	53.53	52,128	60.87	
Age group, years							<0.001
18–40 years	9078	4.12	6822	5.07	2256	2.63	
40–60 years	46,275	21.03	32,167	23.93	14,108	16.47	
60–80 years	97,665	44.38	60,655	45.12	37,010	43.22	
>80 years	67,064	30.47	34,800	25.88	32,264	37.67	
Mean (±SD)	70.15 (15.17)	68.32 (15.41)	73.00 (14.32)	<0.001			
Insurance premium (NT dollars)							<0.001
<20,000	138,504	62.93	79,070	58.81	59,434	69.4	
20,000–40,000	67,567	30.70	45,359	33.74	22,208	25.93	
40,000–60,000	10,328	4.69	7450	5.54	2878	3.36	
>60,000	3683	1.67	2565	1.91	1118	1.31	
Urbanization level							0.004
1 (highest)	53,004	24.08	32,181	23.94	20,823	24.32	
2	60,055	27.29	37,065	27.57	22,990	26.85	
3	36,139	16.42	22,030	16.39	14,109	16.48	
4	36,982	16.80	22,472	16.71	14,510	16.94	
5 (lowest)	33,900	15.40	20,695	15.39	13,205	15.42	
Baseline comorbidities							
HTN	15,0329	68.31	90,837	67.56	59,492	69.47	<0.001
DM	13,6875	62.19	83,590	62.17	53,285	62.22	0.825
CHF	58,264	26.47	32,176	23.93	26,088	30.46	<0.001
COPD	100,444	45.64	58,436	43.46	42,008	49.05	<0.001
CLD	67,061	30.47	40,663	30.25	26,398	30.83	0.004
CKD	82,200	37.35	46,355	34.48	35,845	41.86	<0.001
Cancer	69,432	31.55	35,366	26.31	34,066	39.78	<0.001
CCI score							<0.001
0	4748	2.16	3843	2.86	905	1.06	
1	10,415	4.73	8363	6.22	2052	2.4	
2	11,852	5.39	8744	6.5	3108	3.63	
3	13,081	5.94	9156	6.81	3925	4.58	
≥4	17,9986	81.78	104,338	77.61	75,648	88.33	
Drug use[¶]							
Aspirin	28,861	13.11	16,906	12.57	11,955	13.96	<0.001
Clopidogrel	17,667	8.03	9740	7.24	7927	9.26	<0.001
Warfarin	7325	3.33	4198	3.12	3127	3.65	<0.001
Metformin	48,257	21.93	33,803	25.14	14,454	16.88	<0.001
NSAIDs	151,508	68.84	95,432	70.98	56,076	65.48	<0.001
Statins	20,171	9.17	14,235	10.59	5936	6.93	<0.001
PPIs	91,831	41.73	45,818	34.08	46,013	53.73	<0.001
Steroids	118,048	53.64	59,845	44.51	58,203	67.96	<0.001
Immunosuppressants	1099	0.50	609	0.45	490	0.57	<0.001
Septic shock	111,754	50.78	43,310	32.21	68,444	79.92	<0.001
Endotracheal tube	73,098	33.21	27,647	20.56	45,451	53.07	<0.001
ICU admission	119,912	54.49	58,503	43.51	61,409	71.71	<0.001
Emergent hemodialysis	7600	3.45	2024	1.51	5576	6.51	<0.001
Hospital mortality rate	85,638	38.91					
GI bleeding							<0.001
No	21,1718	96.20	129,952	96.66	81,766	95.48	
Yes	8364	3.80	4492	3.34	3872	4.52	
Stroke							0.104
No	216,701	98.46	132,333	98.43	84,368	98.52	
Yes	3381	1.54	2111	1.57	1270	1.48	

Table 1: Continued.

Variables ($n = 220,082$)	Total		Hospital mortality				P value
			No		Yes		
	n	%	n	%	n	%	
ICH							<0.001
No	218,067	99.08	13,3346	99.18	84,721	98.93	
Yes	2015	0.92	1098	0.82	917	1.07	
AMI							<0.001
No	216,592	98.41	132,830	98.8	83,762	97.81	
Yes	3490	1.59	1614	1.2	1876	2.19	
Infection origins							
Central nervous	1382	0.63	870	0.65	512	0.60	0.153
Respiratory	87,748	39.87	47,674	35.46	40,074	46.79	<0.001
Cardiovascular	1614	0.73	1097	0.82	517	0.60	<0.001
Gastrointestinal/biliary	17,812	8.09	11,914	8.86	5898	6.89	<0.001
Genitourinary	66,518	30.22	50,467	37.54	16,051	18.74	<0.001
Soft tissue/musculoskeletal	10,960	4.98	8409	6.25	2551	2.98	<0.001
Device-related	3712	1.69	2729	2.03	983	1.15	<0.001
Others	17,651	8.02	12,923	9.61	4728	5.52	<0.001
Frequency of OPD visit[#] (median, IQR)	18 (10–27)	17 (10–27)	18 (11–28)				
Frequency of ED visit[#] (median, IQR)	18 (10–27)	17 (10–27)	18 (11–28)				

AMI, acute myocardial infarction; CCI score, Charlson comorbidity index score; CHF, congestive heart failure; CKD, chronic kidney disease; CLD, chronic liver disease; COPD, chronic obstructive pulmonary disease; ED, emergency department; GI, gastrointestinal; HTN, hypertension; ICH, intracranial hemorrhage; ICU, intensive care unit; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug; OPD, outpatient department; PPI, proton pump inhibitor; SD, standard deviation. [¶]Use for more than 1 week within a one-year period prior to the index date. [#]Within a one-year period prior to the index date.

Table 2: Impact of complications on the composite hospital outcomes.

Complications	N	Outcome = hospital mortality			Outcome = ICU admission			Outcome = mechanical ventilation		
		Event n	Event rate	Adjusted OR[¶] (95% CI)	Event n	Event rate	Adjusted OR[¶] (95% CI)	Event n	Event rate	Adjusted OR[¶] (95% CI)
GI bleeding										
No	211,718	81,766	0.39	1 (reference)	114,274	0.54	1 (reference)	69,314	0.33	1 (reference)
Yes	8364	3872	0.46	0.98 (0.93–1.03)	5638	0.67	1.30 (1.23–1.38)***	3784	0.45	1.32 (1.26–1.40)***
Stroke										
No	216,701	84,368	0.39	1 (reference)	117,396	0.54	1 (reference)	71,426	0.33	1 (reference)
Yes	3381	1270	0.38	0.84 (0.78–0.91)***	2516	0.74	2.71 (2.47–2.97)***	1672	0.49	2.07 (1.90–2.25)***
ICH										
No	218,067	84,721	0.39	1 (reference)	118,096	0.54	1 (reference)	71,762	0.33	1 (reference)
Yes	2015	917	0.46	1.08 (0.98–1.19)	1816	0.90	8.02 (6.84–9.42)***	1336	0.66	3.92 (3.52–4.40)***
AMI										
No	216,592	83,762	0.39	1 (reference)	116,758	0.54	1 (reference)	70,941	0.33	1 (reference)
Yes	3490	1876	0.54	1.11 (1.03–1.19)***	3154	0.90	4.78 (4.21–5.42)***	2157	0.62	1.99(1.84–2.16)***

Adjusted OR[¶]: adjusted for age, sex, insurance premium, urbanization level, and comorbidities in the logistic regression model. ***$P < 0.001$.

4.1. Database Validation of the NHIRD. In clinical practice, this is a real-world condition that is encountered every day in the care of sepsis patients. Joint effect analysis provides a useful reference for physicians to predict the probable patient outcomes of sepsis complicated with multiple complications. In this nationwide database, GIB was the most frequent complication, occurred in 3.80% of the patients and followed by AMI in 1.59%, ischemic stroke in 1.54%, and ICH in 0.92%. The accuracy and reproducibility of this study is supported by the comparison with the hospital database (2006–2013) of Taichung Veterans General Hospital, a 1520-bed tertiary referral medical center in central Taiwan. The occurrence rate of GIB and MACEs was similar to that found in this study. In the hospital database, GIB occurred in 5.73% of the sepsis patients, followed by AMI (2.42%), ischemic stroke (1.54%), and ICH (1.22%).

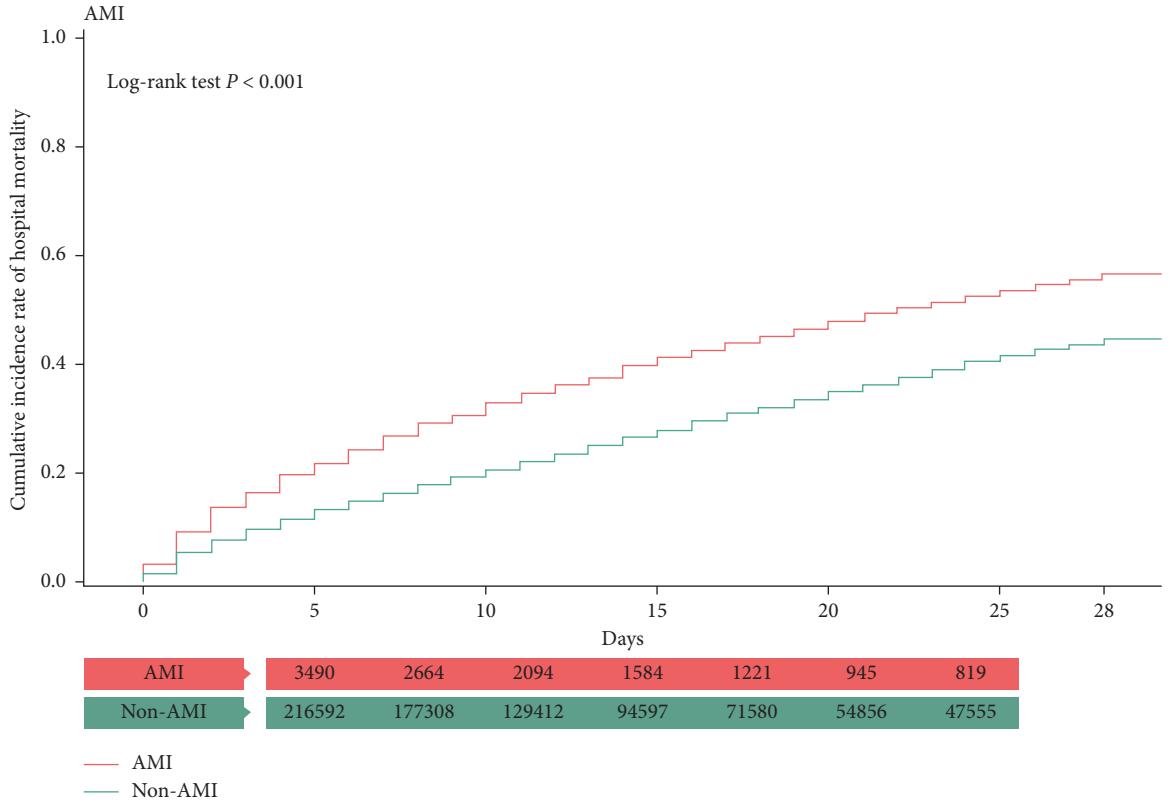

Figure 1: Kaplan–Meier analysis of cumulative hospital mortality in sepsis patients with and without AMI. The differences were evaluated by the log-rank test.

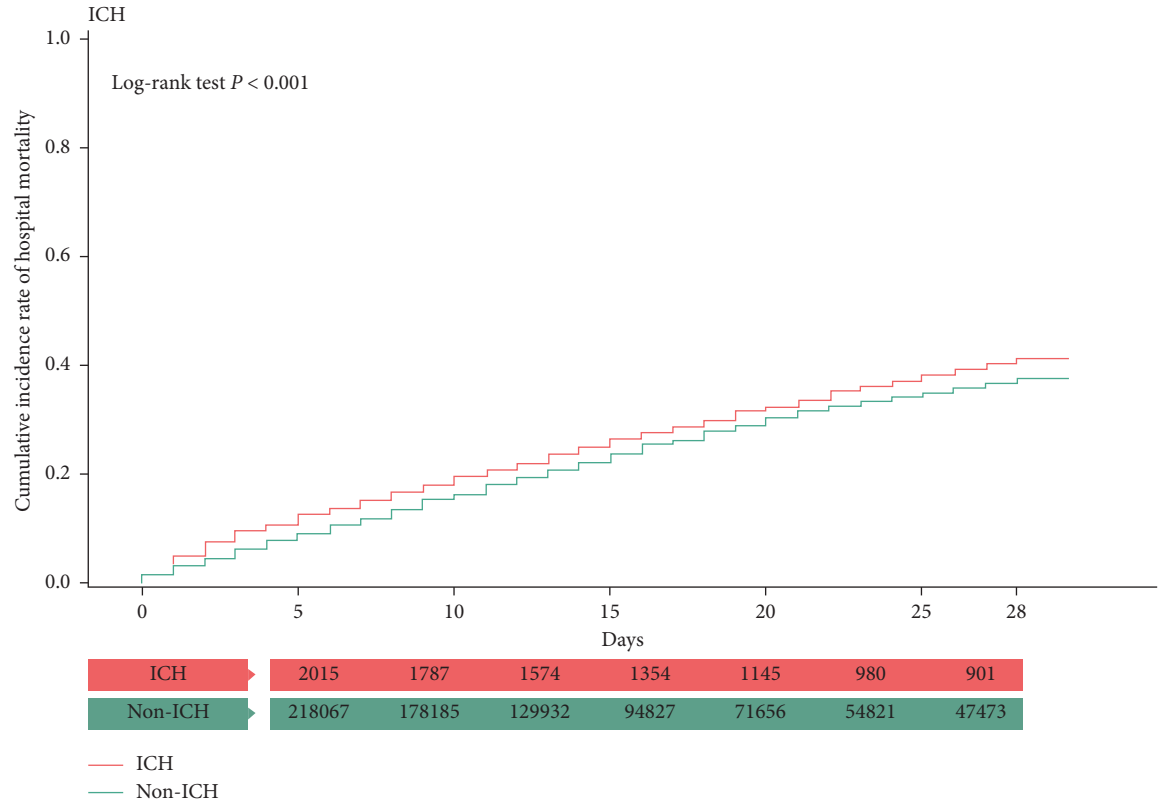

Figure 2: Kaplan–Meier analysis of cumulative hospital mortality in sepsis patients with and without ICH. The differences were evaluated by the log-rank test.

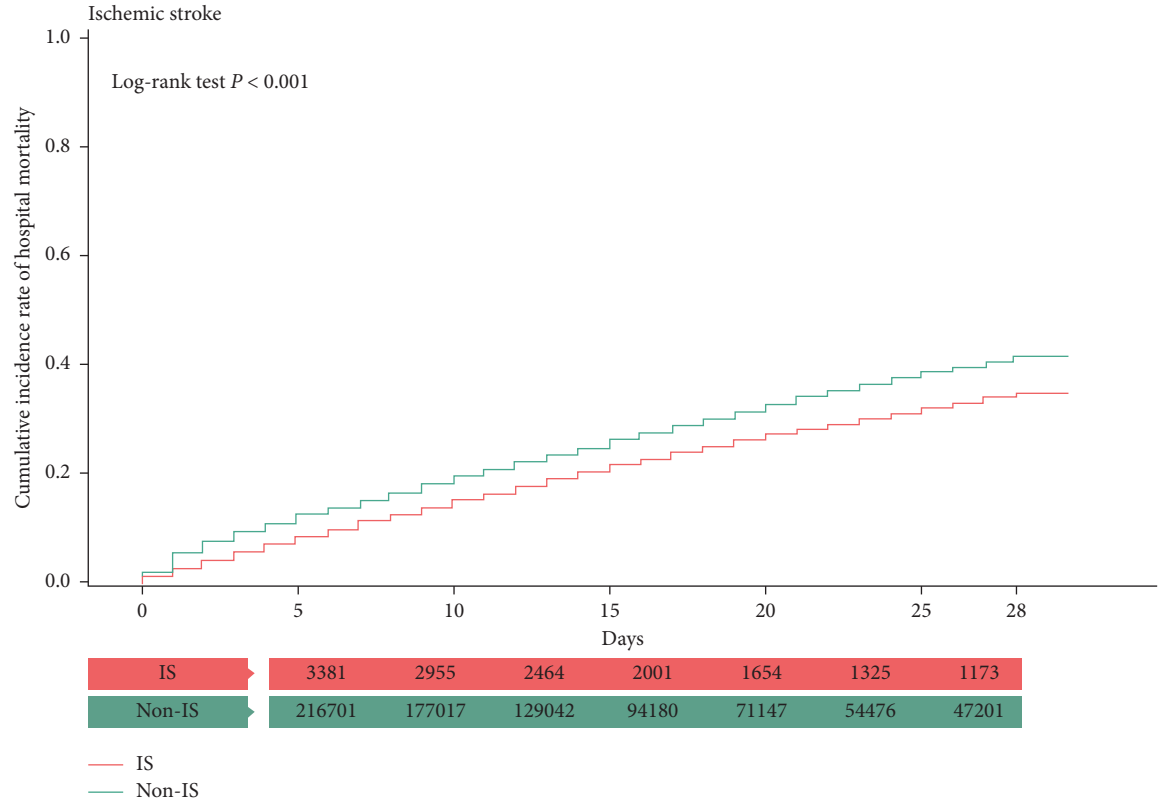

Figure 3: Kaplan–Meier analysis of cumulative hospital mortality in sepsis patients with and without ischemic stroke. The differences were evaluated by the log-rank test.

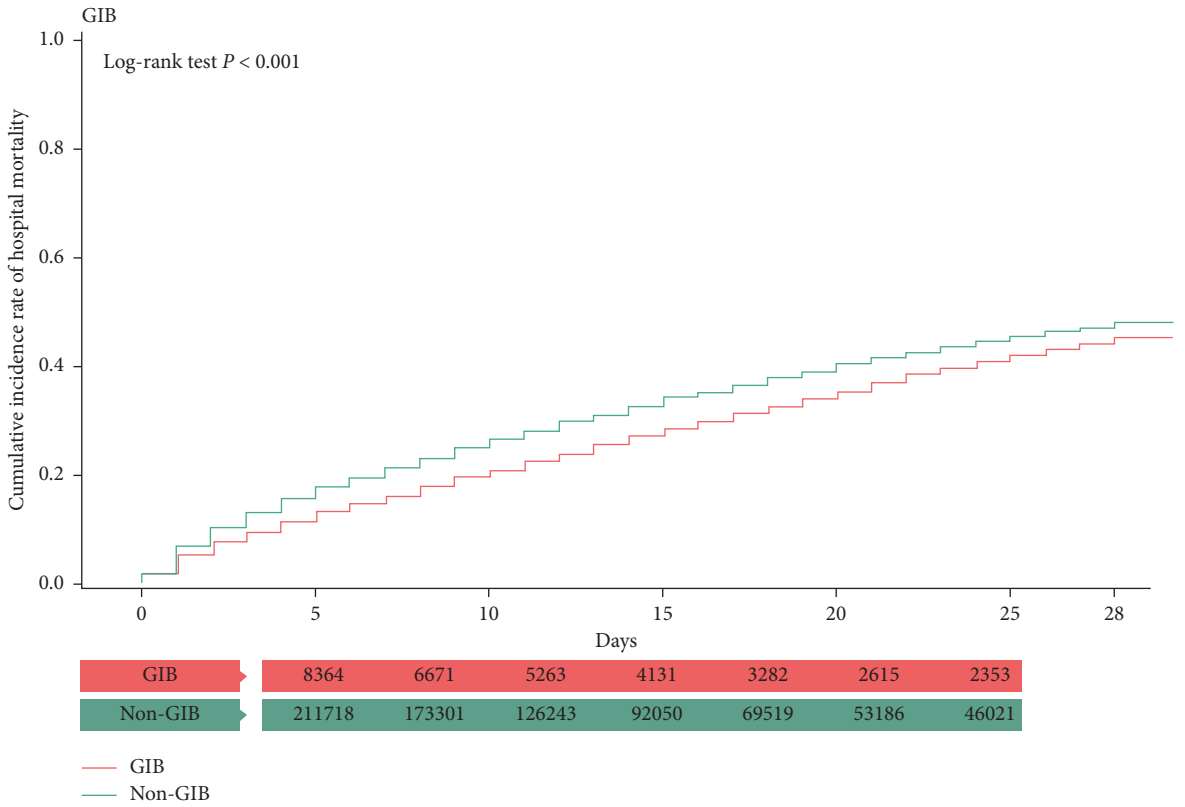

Figure 4: Kaplan–Meier analysis of cumulative hospital mortality in sepsis patients with and without GIB. The differences were evaluated by the log-rank test.

Table 3: Joint effect analyses of association between "hospital mortality, ICU admission, and receiving mechanical ventilation" and "GI bleeding, stroke, ICH, and AMI."

Complications				N	Outcome = hospital mortality			Outcome = ICU admission			Outcome = mechanical ventilation		
GIB	Stroke	ICH	AMI		Event	Event rate	Adjusted OR¶ (95% CI)	Event	Event rate	Adjusted OR¶ (95% CI)	Event	Event rate	Adjusted OR¶ (95% CI)
No	No	No	No	203,522	77,972	0.38	1.00 (reference)	107,413	0.53	1.00 (reference)	64,600	0.32	1.00 (reference)
Yes	No	No	No	7965	3720	0.47	1.01 (0.96–1.07)	5285	0.66	1.30 (1.23–1.38)***	3523	0.44	1.33 (1.26–1.40)***
No	Yes	No	No	2990	1129	0.38	0.89 (0.82–0.97)**	2162	0.72	2.62 (2.38–2.88)***	1427	0.48	2.09 (1.91–2.28)***
No	No	Yes	No	1748	821	0.47	1.17 (1.05–1.30)***	1571	0.90	8.10 (6.84–9.60)***	1158	0.66	4.11 (3.65–4.62)***
No	No	No	Yes	3194	1738	0.54	1.15 (1.06–1.24)**	2882	0.90	4.93 (4.33–5.62)***	1956	0.61	2.03 (1.87–2.21)***
Yes	Yes	No	No	139	44	0.32	0.50 (0.34–0.74)***	118	0.85	3.79 (2.26–6.35)***	81	0.58	2.38 (1.61–3.53)***
Yes	No	Yes	No	106	33	0.31	0.53 (0.34–0.83)**	96	0.91	8.12 (4.00–16.5)***	74	0.70	4.84 (2.96–7.92)***
Yes	No	No	Yes	134	67	0.50	0.82 (0.57–1.18)	119	0.89	3.07 (1.69–5.55)***	92	0.69	2.61 (1.74–3.93)***
No	Yes	Yes	No	115	41	0.36	0.70 (0.46–1.06)	106	0.92	12.41 (5.99–25.71)**	72	0.63	3.42 (2.18–5.36)***
No	Yes	No	Yes	112	46	0.41	0.68 (0.46–1.03)	106	0.95	12.28 (5.10–29.56)***	77	0.69	3.48 (2.18–5.57)***
No	No	Yes	Yes	31	16	0.52	1.05 (0.49–2.23)	29	0.94	7.37 (1.59–34.13)***	22	0.71	3.29 (1.37–7.91)**

Adjusted OR: adjusted for age, sex, insurance premium, urbanization level, and comorbidities in the logistic regression model. ** $P < 0.01$; *** $P < 0.001$. AMI, acute myocardial infarction; CI, confidence interval; GIB, gastrointestinal bleeding; ICH, intracranial hemorrhage; OR, odds ratio.

4.2. AMI during Sepsis. An analysis of a national database in the USA by Smilowitz et al. in 2016 found that 118,183 of 2,602,854 sepsis inpatients (4.5%) had a concurrent diagnosis of AMI during hospitalization. The hospital mortality was higher in sepsis patients with concurrent AMI (aOR = 1.24), which is in line with our finding of an aOR of 1.11 (95% CI, 1.03–1.19) for sepsis complicated by AMI [10]. Both studies found that AMI not only complicated the sepsis course but was also associated with a significant increase in total hospital mortality. Smilowitz et al. reported that patients who were managed more invasively had much lower mortality than those managed conservatively.

4.3. Ischemic Stroke and ICH. Acute ischemic and hemorrhagic strokes are the fifth leading cause of death in the United States, and those who survive with subsequent long-term disabilities cause a heavy national socioeconomic burden [19]. Chronic hypertension, DM, atherosclerotic disease, and exposure to environmental toxins including air pollution have been identified as risk factors. A case-crossover study by Amelia et al. found that recent hospitalization for infection was associated with an increased risk of stroke, and that severe sepsis was associated with new-onset atrial fibrillation, which also increased stroke risk [20]. A population-based cohort study of inpatients in Denmark found that about 80% of the cardiovascular events in those admitted with bacteremia occurred within 6 months [21].

4.4. GIB during Sepsis. A database analysis of patients with septic shock in the USA by Siddiqui et al. reported that the incidence of GIB was 5.4% (6,571/119,684) in those hospitalized patients between 2003 and 2012. The occurrence of GIB was associated with a 9% increase in mortality from 45% to 54% [5]. In this study, the GIB occurred in 3.80% of the patients, and the occurrence of GIB increased mortality to 46% compared with 39% in uncomplicated sepsis. However, the adjusted OR did not find a significant association of GIB with an increased risk of mortality (aOR = 0.98, 95% CI, 0.93–1.03)). GIB is not an infrequent complication of sepsis patients, and it increases the complexity of care. Siddiqui et al. found that GIB increased the length of hospital stay from 15.76 to 20.56 days [5]. Consequently, effective GIB prophylaxis is important, and PPIs may be of use. A randomized controlled trial by Krag et al. comparing pantoprazole and placebo in critically ill patients at risk of GIB found that 90-day mortality. However, pantoprazole reduced the occurrence of clinically important GIB from 4.2% to 2.5% of the patients [22]. Although PPIs can prevent clinically important GIB, a recent meta-analysis by Alhazzani et al. concluded that routine use for stress ulcer prophylaxis may increase the risk of pneumonia, leaving their use during sepsis open to question [23]. A subsequent network meta-analysis by Wang et al. on the relationship of GIB and septic shock is in line with the results of this study that GIB increased the

complexity of sepsis case management but did not influence hospital mortality [18].

4.5. Concurrence of GIB and MACEs. Joint effect analysis found that no combination of any two GIB and MACE complications had a significant effect on mortality as we previously thought, but any combination significantly increased the complexity of the sepsis course and the incidence of respiratory failure. If GIB or MACE complications were caused by sepsis and can be improved or resolved by supplemental therapy or prophylaxis, the complexity of the sepsis course would be reduced. However, hospital mortality would remain unchanged under the current best supportive care.

4.6. Limitations. This study had some limitations, but they did not detract from the correctness of our main study results. First, as a large epidemiologic study using an administrative database, it was inevitably lacking in laboratory data such as inflammatory markers and lactate levels. Composite outcomes, including total hospital mortality, ICU admission (a proxy of critical condition), and receiving MV (a proxy of respiratory failure), were used to estimate the impacts of GIB and MACE during sepsis because they were not affected by the laboratory data alone, but those outcomes reflected poor laboratory data. Second, in the administrative database, we could not distinguish whether PPIs were used for ulcer treatment or prophylaxis. However, prophylactic PPI use did not play a role in the sepsis course [24]. Third, different pathogens, such as bacteria, virus, and fungus, can influence the occurrence of associated complications. For example, systemic salmonella infection may cause abdominal aortic infected aneurysm [25]. However, in the NHIRD, information on the definite pathogen that caused sepsis was unavailable, except for some rare specific codings, for example, ICD-9-CM: 481, pneumococcal pneumonia; ICD-9-CM: 002, typhoid/paratyphoid fever; ICD-9-CM: 01, pulmonary tuberculosis [16].

5. Conclusion

GIB and MACE were associated with a significantly increased risk of ICU admission and MV but not with total hospital mortality, which was independently associated with AMI or ICH alone. Early prevention of GIB and MACEs can at least reduce the complexity of clinical course and even the hospital mortality.

Abbreviations

AMI: Acute myocardial infarction
CI: Confidence interval
GIB: Gastrointestinal bleeding
ICD-9-CM: International classification of diseases, ninth revision, clinical modification
ICH: Intracranial hemorrhage
ICU: Intensive care unit
MACE: Major adverse cardiovascular event
NHIA: National Health Insurance Administration
NHIRD: National Health Insurance Research Database
OR: Odds ratio
PPI: Proton pump inhibitor.

Data Availability

The data that support the findings of this study are available from the LHDB but restrictions apply to the availability, which were used under license for the current study. They are not publicly available but are available from the corresponding author upon reasonable request.

Additional Points

Novelty Statement. This study contributed at least several important novelties in clinical practice. (1) Here, we used the nationwide database of 15 years, from 1999 to 2013, including 220,082 patients, first admitted for sepsis to examine the impacts of two major common complications during sepsis, including gastrointestinal bleeding (GIB) and major adverse cardiovascular events (MACEs) on the hospital outcome. (2) We conducted the multivariate analysis to analyze the odds ratio of every complication on sepsis outcomes, including the hospital mortality, intensive care unit admission, and receiving mechanical ventilation. (3) Joint effect analysis of every complication of GIB and MACEs was conducted to clarify their interactions during sepsis.

Ethical Approval

This study analyzed data retrieved from a longitudinal cohort of diabetes patients (LHDB) in Taiwan. As the LHDB contains deidentified secondary data for research, the study was exempted from the requirement of informed consent from participants. The institutional review boards of China Medical University (CMUH104-REC2-115) and Taichung Veterans General Hospital (CE18102A) approved the study.

Disclosure

The funders had no role in the study design, data collection, analysis, decision to publish, or preparation of the manuscript.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Authors' Contributions

Ming-Shun Hsieh proposed and designed the study. Shu-Hui Liao and Vivian Chia-Rong Hsieh were responsible for data analysis and interpretation. Ming-Shun Hsieh wrote the manuscript. Chorng-Kuang How performed critical revisions and approved the final version of the manuscript. All

authors have read and approved the final manuscript for publication.

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Research Article

Comparison of Dopamine and Norepinephrine Use for the Treatment of Hypotension in Out-Of-Hospital Cardiac Arrest Patients with Return of Spontaneous Circulation

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In patients experiencing out-of-hospital cardiac arrest (OHCA), hypotension is common after return of spontaneous circulation (ROSC). Both dopamine and norepinephrine are recommended as inotropic therapeutic agents. This study aimed to determine the impact of the use of these two medications on hypotension. This is a multicenter retrospective cohort study. OHCA patients with ROSC were divided into three groups according to the post resuscitation inotropic agent used for treatment in the emergency department, namely, dopamine, norepinephrine, and dopamine and norepinephrine combined therapy. Thirty-day survival and favorable neurologic performance were analyzed among the three study groups. The 30-day survival and favorable neurologic performance rates in the three study groups were 12.5%, 13.0%, and 6.8% as well as 4.9%, 4.3%, and 1.2%, respectively. On controlling the potential confounding factors by logistic regression, there was no difference between dopamine and norepinephrine treatment in survival and neurologic performance (adjusted odds ratio (aOR): 1.0, 95% confidence interval (CI) 0.48–2.06; aOR: 0.8, 95% CI: 0.28–2.53). The dopamine and norepinephrine combined treatment group had worse outcome (aOR: 0.6, 95% CI: 0.35–1.18; aOR: 0.2, 95% CI: 0.05–0.89). In conclusion, there was no significant difference in post-ROSC hypotension treatment between dopamine and norepinephrine in 30-day survival and favorable neurologic performance rates.

1. Introduction

In patients developing out-of-hospital cardiac arrest (OHCA), hypotension often occurs within minutes to hours of return of spontaneous circulation (ROSC) [1, 2]. Post-ROSC hypotension is a predictor of in-hospital death and is associated with diminished functional status among survivors [3, 4]. Therefore, post-ROSC hypotension should be treated aggressively. Dopamine and norepinephrine are both commonly used inotropic therapeutic agents for hypotension [5]. Norepinephrine is a naturally occurring potent vasoconstrictor and an inotropic agent. Dopamine is a catecholamine-like agent and a chemical precursor of norepinephrine that has both α-receptor- and β-receptor-stimulating actions. Currently, Backer et al. reported that the use of dopamine was associated with a greater number of adverse events for shock patients [5]. In patients with septic shock, norepinephrine is preferred to dopamine. This is because dopamine is associated with greater mortality and has a higher incidence of arrhythmic events than that of norepinephrine [6]. However, there is no evidence demonstrating the

superiority of any one vasopressor in the postcardiac arrest patient. In this study, we aimed to determine the impact of the use of dopamine and norepinephrine on hypotension in ROSC patients.

2. Materials and Methods

This multicenter retrospective cohort study was approved by the Institutional Review Board of the Chang Gung Medical Foundation (201600794B0). All patients' records and information were anonymized and deidentified before analysis.

This study was conducted in five emergency departments (EDs) within the same healthcare system in Taiwan, between January 2010 and December 2014. Two EDs were located in a tertiary referral medical center, whereas the other three were situated in secondary regional hospitals. All adult patients (older than 18 years old) who presented to the EDs with nontraumatic cardiac arrest and developed sustained ROSC (when chest compressions are not required for 20 consecutive minutes and signs of circulation persist) with inotropic agent therapy (dopamine or norepinephrine) were included in this study [7, 8]. Patients with a do-not-resuscitation order were excluded.

Demographic data and baseline medical conditions related to Charlson comorbidity index [9], including a history of myocardial infarction, heart failure, cerebrovascular accident, chronic obstructive pulmonary disease, renal and liver disease, and malignancy as well as ED resuscitation records, were extracted from the ED administrative database of participating hospitals [10].

In the five EDs, OHCA patients developing post-ROSC hypotension were treated according to the standard advanced cardiovascular life support (ACLS) protocol. Patients were divided into three groups according to the postresuscitation inotropic agent used in EDs, namely, dopamine, norepinephrine, and dopamine and norepinephrine combined therapy. The primary outcome was 30-day survival. The secondary outcome was favorable neurologic performance, which was according to the Cerebral Performance Category (CPC), with scores 1 and 2 [7]. Two other resuscitation medication doses including epinephrine and sodium bicarbonate were also counted. The dose of epinephrine was 1 mg per vial and that of sodium bicarbonate was 16.7 meq per vial. The relationships between the three study groups and primary and secondary outcomes and the two resuscitation medications were analyzed.

For continuous variables, the data were summarized as means and standard deviations (SD) or medians with interquartile ranges (IQRs) if the data were not normally distributed. The categorical demographic factors were presented as numbers and percentages. Analysis of variance, nonparametric Kruskal–Wallis, and chi-squared tests were used for analyses. To control the potential confounding factors, binomial and multinomial logistic regression analyses were conducted to analyze the relationship between inotropic agent therapy and outcome and the association between inotropic agent therapy and epinephrine and sodium bicarbonate. The effects were estimated in terms of adjusted odds ratios (aORs) and the corresponding 95% confidence intervals (CIs). Significance testing was two-sided, and $p < 0.05$ was considered to indicate statistical significance. SPSS version 12.0 (SPSS, Chicago, IL) was used for all statistical analyses.

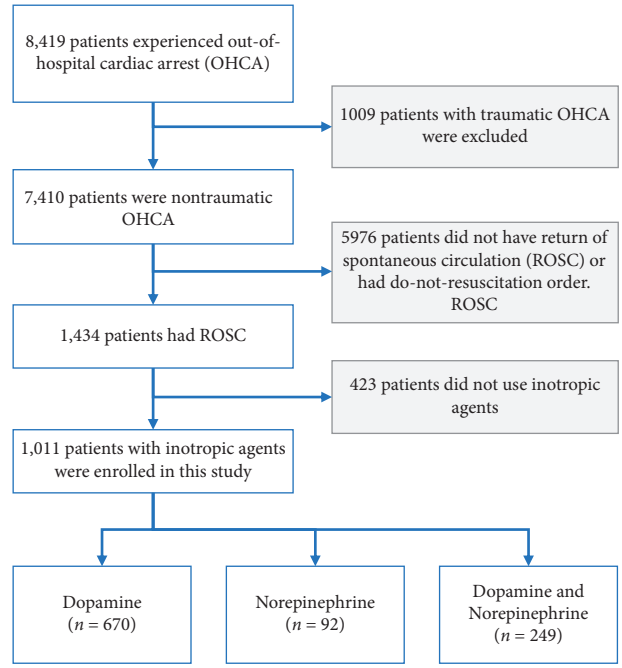

Figure 1: Flowchart of the patient selection process. The patients were included in the study based on the criteria shown above and were divided into three treatment groups.

3. Results

In total, 7410 nontraumatic OHCA patients visited the five EDs during the study period. Among them, 1434 (19.4%) developed ROSC, and 1011 (13.6%) developed post-ROSC hypotension. Among the posthypotension patients, 669 (66.2%) survived to intensive care unit (ICU) admission, and 225 had 30-day survival. Patients who developed ROSC were divided into three treatment groups (Figure 1). There were 670 with dopamine, 92 with norepinephrine, and 249 with dopamine and norepinephrine combined therapy. Table 1 shows patients' demographics, comobility, Charlson Comorbidity Index, status upon arrival, and treatment type in the EDs in the three study groups. Figures 2 and 3 show the survival curve and the rates of 30-day survival and favorable neurologic performance. While patients who needed both dopamine and norepinephrine combined therapy after resuscitation had worse survival rate and neurologic outcome, the outcomes in the dopamine and norepinephrine groups were similar.

To control the potential confounding factors, binomial logistic regression analyses were conducted. Table 2 shows the outcome of regression. With increasing age, patients tended to have a lower survival rate and poorer neurologic

Table 1: Characteristics of patients treated with different inotropic agents after return of spontaneous circulation.

	Dopamine ($n = 670$)	Norepinephrine ($n = 92$)	Dopamine + Norepinephrine ($n = 249$)	p-value
Age	68.7 ± 15.87	66.4 ± 18.02	68.1 ± 16.26	0.438
Male	367 (54.8%)	52 (56.5%)	138 (55.4%)	0.989
Comobility				
Heart failure	92 (13.7%)	10 (10.9%)	26 (10.4%)	0.355
CVA	136 (20.3%)	25 (27.2%)	53 (21.3%)	0.318
COPD	165 (24.6%)	16 (17.4%)	47 (18.9%)	0.083
DM	194 (29.0%)	32 (34.8%)	84 (33.7%)	0.252
Renal disease	131 (19.6%)	11 (12.0%)	33 (13.3%)	0.029
Liver cirrhosis	85 (12.7%)	11 (12.0%)	30 (12.0%)	0.955
Malignancy	89 (13.3%)	13 (14.1%)	40 (16.1%)	0.559
CCI	3 ± 1.5	2 ± 2.0	3 ± 1.5	0.574
Status upon arrival				
EMT transfer	482 (71.9%)	73 (79.3%)	178 (71.5%)	0.302
Shockable rhythm	71 (10.6%)	14 (15.2%)	21 (8.4%)	0.190
Treatment in ED				
Epinephrine (mg)	5 ± 2.5	5 ± 2.0	7 ± 3.5	<0.001
Sodium bicarbonate (vial)	4 ± 4.0	4 ± 4.5	8 ± 5.0	<0.001
PCI	28 (4.2%)	4 (4.3%)	5 (2.0%)	0.278
ECMO	7 (1.0%)	2 (2.2%)	1 (0.4%)	0.330
ICU admission	475 (70.9%)	66 (71.7%)	146 (58.6%)	0.001

CVA: cerebrovascular accident; COPD: chronic obstruction pulmonary disease; DM: diabetes mellitus; EMT: emergency medical technician; shockable rhythm: ventricular fibrillation and pulseless ventricular tachycardia; ED: emergency department; PCI: percutaneous coronary intervention; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit.

outcome. Patients presenting to EDs with shockable rhythms had higher a 30-day survival rate but no more favorable neurologic result. Increasing use of epinephrine and sodium bicarbonate was associated with lower 30-day survival but not related to good neurologic performance. Finally, during the postresuscitation period, compared with patients who received dopamine treatment alone, patients who needed both dopamine and norepinephrine combined therapy had a poor neurologic outcome. There was no significant difference between patients who used dopamine and norepinephrine.

Table 3 shows the relationship between resuscitation medications (epinephrine and sodium bicarbonate) and postresuscitation inotropic agent therapy. Patients receiving more sodium bicarbonate therapy had a higher chance of requiring dopamine and norepinephrine combined therapy during the postresuscitation period.

4. Discussion

ROSC after OHCA is characterized by myocardial stunning and a robust systemic proinflammatory response [11]. Trzeciak et al. reported that post-ROSC hypotension is a predictor of in-hospital death and is associated with diminished functional status among survivors [3]. This finding is in line with that of our research. Clinically, increased use of inotropic agents during the postresuscitation period indicated that these patients had a more unstable haemodynamic presentation. In our study, patients who needed both dopamine and norepinephrine after ROSC had lower 30-day survival and favorable neurologic performance rates than those who needed only one inotropic agent. We believe that it might be related because these patients were sicker than those in the other groups. On the other hand, the overall survival rate was obviously lower in our study, and this might partially be due to the type of study population. Stephen et al. reported the data of patients admitted to the ICU. In our study, only 66.2% patients had survival to ICU admission. This might have influenced the outcome.

Recently, some studies suggested norepinephrine is superior to dopamine for the treatment of shock. Backer et al. reported an increased 28-day mortality among patients with cardiogenic shock when treated with dopamine as compared with that in treatment with norepinephrine [5]. A meta-analysis reported that dopamine, compared with norepinephrine, was associated with a higher incidence of arrhythmias and with an increased risk of death in patients with septic shock [6]. Rui et al. reported that norepinephrine was associated with a lower 28-day mortality, lower risk of arrhythmic events, and gastrointestinal reaction [12]. There was no suggestion about post-ROSC hypotension. According to our study, when comparing the 30-day survival and favorable neurologic outcome between the dopamine and norepinephrine groups, there was no significant difference. However, in our study, fewer patients were treated with norepinephrine than those treated with dopamine. The reason for why there were more patients given dopamine as compared with receiving norepinephrine is that, in general, dopamine is the first line vasopressor that would be used amongst practitioners of the 5 emergency departments involved in our study. This might have influenced the analysis of the outcome.

Post-ROSC therapy is a crucial link in the "Chain of Survival" paradigm for treating cardiac arrest [13]. However, some types of resuscitation treatments might

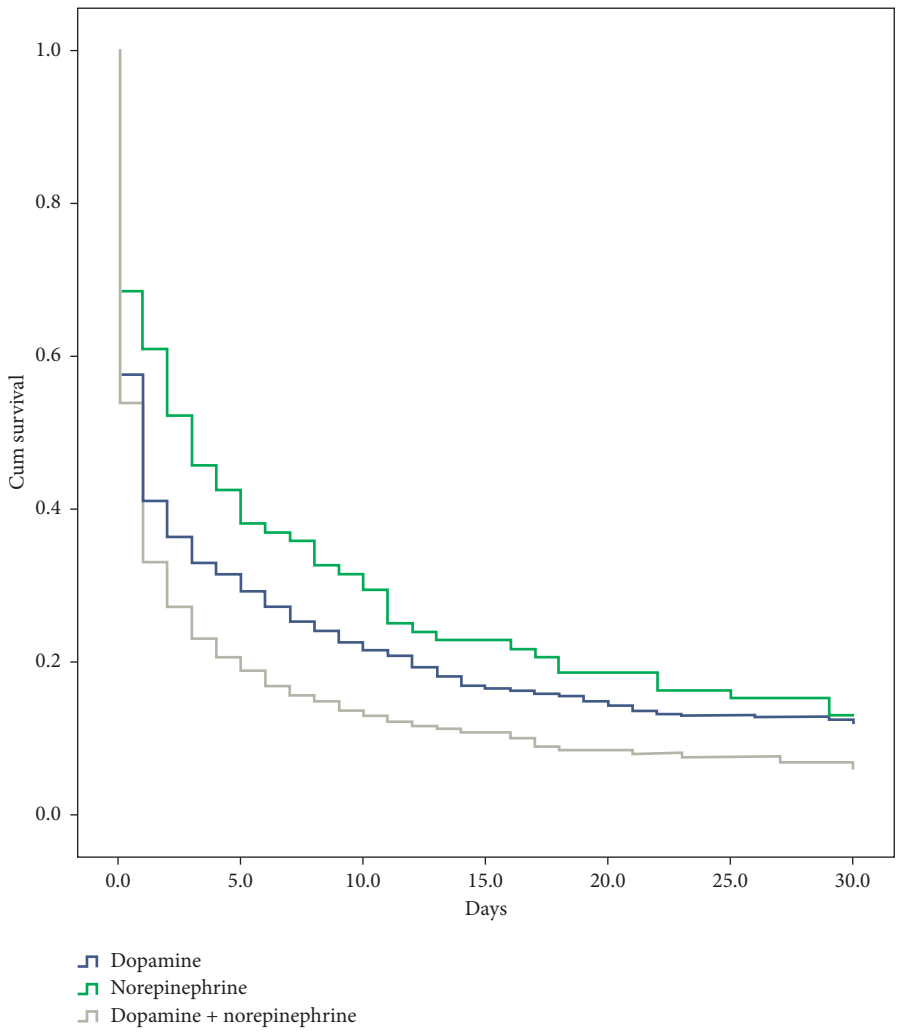

Figure 2: Survival curves of the three treatment groups. Compared with the dopamine treatment group (blue line), the p values were 0.128 (norepinephrine) (green line) and 0.002 (dopamine + norepinephrine) (gray line).

also influence the post-ROSC hemodynamic performance. Prolonged ventricular fibrillation is related to post-resuscitation hypotension [14]. Severe metabolic acidosis is associated with refractory shock [15]. In our study, we counted the dose of epinephrine and sodium bicarbonate. The epinephrine dose is related to the resuscitation duration, and sodium bicarbonate is associated with the degree of acidosis. Owing to the retrospective nature of the study, which is a potential limitation, the data of some parameters such as cardiopulmonary resuscitation duration and blood gas analysis were not available in the medical records, but information on the two medications might provide us further important information. Patients who received more sodium bicarbonate had higher chance of needing combined inotropic agent use. These findings were also compatible with those of the previous research in this area.

There are some limitations of this study. The retrospective nature of the study made it difficult to assemble the data; hence, there was no stratified analysis according to the etiology. There was no prehospital information and long-term follow-up after discharge. In the study hospitals, prehospital information was not included as part of hospital electronic medical records; therefore, the analysis did not consider this. However, some patients were not brought by emergency medical technicians, but by their family; they might not have received basic life support during transportation. Treating postcardiac arrest hypotension should include fluid resuscitation, but we did not have data about fluid treatment. We did not know the total inotropic dose which patients received and intravenous (IV) route either. Unlike epinephrine which is administered often as an IV shot during resuscitation, dopamine and norepinephrine administration was a continuous IV drip, making it difficult to calculate the dose. We had no laboratory data and vital signs before and after each treatment, and the number of patients who received norepinephrine therapy was much fewer than that in the other study groups which might have influenced the data analysis. Finally, although it was a multicenter study, the five study EDs belonged to the same healthcare system, potentially limiting the implications of the results.

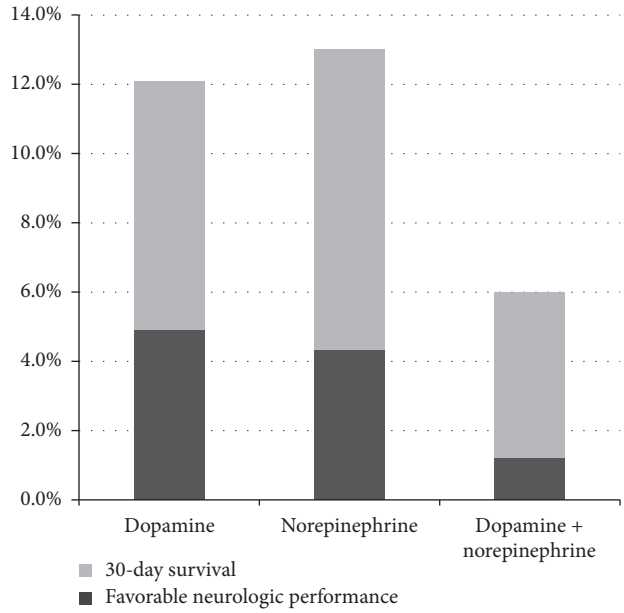

Figure 3: Thirty-day survival and favorable neurologic performance rates in the three study groups. Thirty-day survival rates: 12.1%, 13.0%, and 6.0% ($p = 0.022$); favorable neurologic performances: 4.9%, 4.3%, and 1.2% ($p = 0.036$).

Table 2: Association of postresuscitation inotropic agent therapy and 30-day survival and favorable neurologic performance.

	30-day survival		Favorable neurologic performance	
	aOR	95% C.I.	aOR	95% C.I.
Age	0.96	0.942~0.972	0.95	0.929~0.974
Male	1.0	0.65~1.67	1.8	0.84~3.90
Charlson comorbidity index	1.0	0.91~1.12	1.0	0.87~1.20
Shockable rhythm	2.1	1.12~4.11	1.6	0.56~4.35
Epinephrine	0.9	0.89~0.99	1.0	0.88~1.04
Sodium bicarbonate	0.95	0.912~0.996	1.0	0.94~1.06
Postresuscitation inotropic therapy				
Dopamine	1			1
Norepinephrine	1.0	0.48~2.06	0.8	0.28~2.53
Dopamine + norepinephrine	0.6	0.30~1.10	0.2	0.04~0.78

Shockable rhythm: ventricular fibrillation and pulseless ventricular tachycardia; aOR: adjusted odds ratio; CI: confidence interval.

Table 3: Association between postresuscitation inotropic agent therapy and resuscitation medication.

	Dopamine		Norepinephrine		Dopamine + norepinephrine	
	aOR	95% C.I.	aOR	95% C.I.	aOR	95% C.I.
Epinephrine	1	—	1.0	0.90~1.02	1.0	1.00~1.06
Sodium bicarbonate	1	—	1.0	0.95~1.04	1.1	1.05~1.11

Adjusted for age, sex, Charlson Comorbidity Index, and cardiac rhythm in multinomial logistic regression. aOR: adjusted odds ratio; CI: confidence interval.

5. Conclusions

In conclusion, our study did not show any significant difference in post-ROSC hypotension treatment between dopamine and norepinephrine in 30-day survival rate and favorable neurologic performance. Patients needing combined inotropic agents had poor prognosis. Increasing use of bicarbonate during resuscitation was associated with post-ROSC hypotension needing combined inotropic agent therapy.

Data Availability

The data used to support the findings of this study have not been made available, because, according to the policy of the Institutional Review Board of the Chang Gung Medical

Foundation, the patients' data should not be made publicly available.

Conflicts of Interest

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

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