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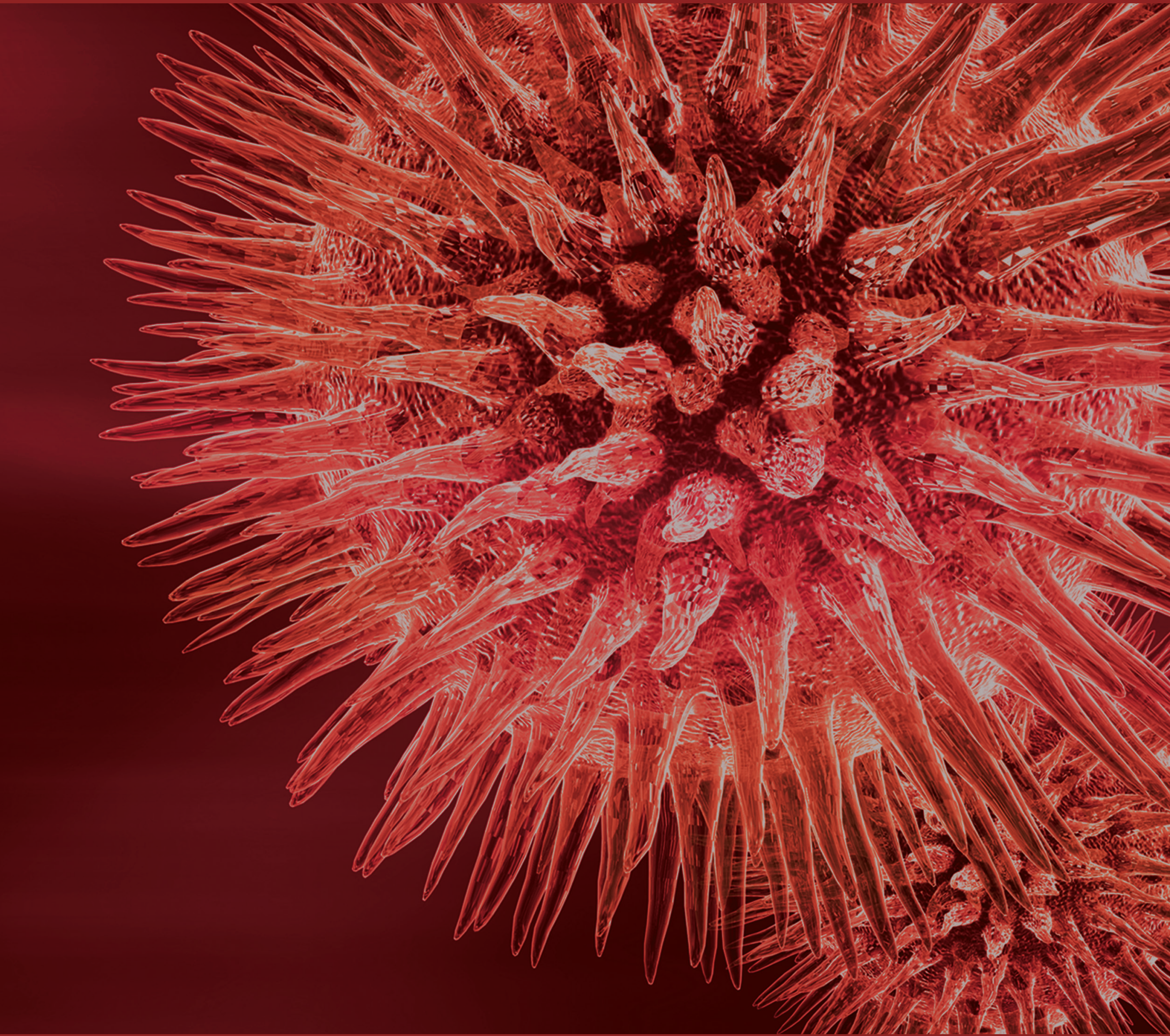
Cardiovascular Emergencies

Lead Guest Editor: Yu-Jun Chang
Guest Editors: Shih-Lin Chang, Eric Chong, Kazuyoshi Suenari, and Antonios Michalopoulos



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Editorial

Cardiovascular Emergencies

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Cardiovascular disease is the most prevalent disease worldwide. It is the leading global cause of death, accounting for 15 million deaths in 2015 [1]. Cardiovascular disease often presents in emergency situations; prompt treatment is essential to reduce mortality. "Time is gold" has always been the cornerstone of cardiovascular emergency management, as every 30-minute delay in door to balloon time translates into 7.5% relative increase in mortality [2]. Rapid evolution in knowledge, technology, and healthcare system efficiency play important roles in saving patients' lives during cardiovascular emergencies. The common treatment goal is to shorten the door to balloon time; rapid ambulance transfer service, early emergency department triage, and seamless team work are key factors in lowering the door to balloon time to new limit.

Today, acute ST elevation myocardial infarction, cardiogenic shock, and out-of-hospital cardiac arrest are the most life-threatening cardiovascular emergencies. Many attempts have been made to improve the healthcare system and efficacy to lower the mortality further. In this special issue, internationally renowned authors shared their invaluable research in management of cardiac arrest, acute myocardial infarction, and cardiogenic shock. The data on prognostic analysis of cardiogenic shock during acute myocardial infarction are being presented. The data and advantage of further reduction in door to balloon time during primary coronary intervention to less than 60 min compared to over 60–90 min are being addressed. The public knowledge of bystander cardiopulmonary resuscitation and, in particular, the nurse's role for saving on-scene time for out-of-hospital collapse are being examined in detail. Further public awareness campaign and hospital workflow can be proposed based on these valuable data.

Out-of-hospital cardiac arrest is one of the most dreadful conditions leading to over 90% mortality rate [3]; for patients being resuscitated on time and restoring spontaneous circulation, many develop cardiogenic shock requiring inotropic and mechanical support beyond emergency revascularization. Aggressive adjunctive treatments are required to promptly correct hypoxia, normalize acidosis and electrolytes imbalance, improve cardiac output, and revert multiorgan failure. Cooling therapy plays additional role in reducing hypoxic brain injury [4]. In this special issue, novel treatment strategies including the utilization of glutamine to protect against postarrest acidosis are being discussed. Invaluable experience on hemodynamic analysis of pediatric cardiogenic shock using transpulmonary thermodilution is being highlighted.

This special issue provides the readers with deeper insight into the management of high risk cardiovascular emergencies and the topics are highly interest-generating and are scientifically valid.

Yu-Jun Chang
Shih-Lin Chang
Eric Chong
Kazuyoshi Suenari
Antonios Michalopoulos

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Research Article

The Association between Door-to-Balloon Time of Less Than 60 Minutes and Prognosis of Patients Developing ST Segment Elevation Myocardial Infarction and Undergoing Primary Percutaneous Coronary Intervention

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Background. The study aimed to verify the effect of primary percutaneous coronary intervention (PPCI) with <60 min door-to-balloon time on ST segment elevation myocardial infarction (STEMI) patients' prognoses. *Methods.* Outcomes of patients receiving PPCI with door-to-balloon time of <60 min were compared with those of patients receiving PPCI with door-to-balloon time 60–90 min. *Result.* Totally, 241 STEMI patients (191 with Killip classes I or II) and 104 (71 with Killip classes I or II) received PPCI with door-to-balloon time <60 and 60–90 min, respectively. Killip classes I and II patients with door-to-balloon time <60 min had better thrombolysis in myocardial infarction (TIMI) flow (9.2% fewer patients with TIMI flow <3, $p = 0.019$) and 8.0% lower 30-day mortality rate ($p < 0.001$) than those with 60–90 min. After controlling the confounding factors with logistic regression, patients with door-to-balloon time <60 min had lower incidences of TIMI flow <3 (aOR = 0.4, 95% CI = 0.20–0.76), 30-day recurrent myocardial infarction (aOR = 0.3, 95% CI = 0.10–0.91), and 30-day mortality (aOR = 0.3, 95% CI = 0.09–0.77) than those with 60–90 min. *Conclusion.* Door-to-balloon time <60 min is associated with better blood flow in the infarct-related artery and lower 30-day recurrent myocardial infarction and 30-day mortality rates.

1. Introduction

The American Heart Association guidelines suggest primary percutaneous coronary intervention (PPCI) as the preferred treatment for ST segment elevation myocardial infarction (STEMI) patients [1]. For nontransfer patients, PPCI should be performed within 90 min of arrival at a hospital. The door-to-balloon time is strongly associated with the likelihood of survival and is an accepted measure of care quality [2, 3]. Multiple strategies have been utilized to reduce the door-to-balloon time [4–6]. However, recently, some studies have reported that significantly shortened door-to-balloon time may not improve the mortality rate of STEMI patients who are undergoing PPCI [7, 8]. This finding raises the question of whether shortening of the door-to-balloon interval is necessary. Since the 2012 European Society of Cardiology guidelines suggested that the goal should be to achieve a door-to-balloon time of less than 60 min of presentation in PPCI-capable institutions [9], few studies have focused on the effect of <60 min door-to-balloon time on the outcome of STEMI patients. Recently, Wang et al. (2016) reported that <60 min door-to-balloon time is associated with better survival rates in younger STEMI patients undergoing PPCI than in their elderly counterparts [10]. However, this study also included patients undergoing PPCI with >90 min door-to-balloon time, which might have influenced the results. Our study focused on the difference between door-to-balloon times of <60 min and 60–90 min, which could help to determine whether further shortening of the door-to-balloon time is necessary.

2. Methods

2.1. Study Design. This retrospective study was approved by the Chang Gung Medical Foundation Institutional Review Board. All data in the patient and physician records were anonymized and deidentified. The research protocol was approved by the Ethics Committee, and a waiver of informed consent was granted.

2.2. Study Setting and Participants. This study was conducted in a 3000-bed tertiary referral medical center located in Kaohsiung City in Southern Taiwan. Over 130,000 patients visit the emergency department (ED) annually. More than 150 STEMI patients (including transfer and nontransfer patients) are treated each year, nearly all of whom receive PPCI as a reperfusion therapy. STEMI patients receiving PPCI between January 1, 2011, and December 31, 2014, were included in this study. Patients aged ≥18 years who arrived at the ED within 12 h of symptom onset and met the diagnostic criteria of acute STEMI assessed through electrocardiogram (ECG) (ST segment elevation > 1 mm in two contiguous limb leads and 2 mm in precordial leads or the presence of new-onset left bundle branch block) [11] and coronary artery disease confirmed by PPCI were included. We excluded patients with >90 min door-to-balloon time and those with prolonged cardiopulmonary resuscitation in the ED because of their expected poor outcomes. Patients referred from other hospitals were also excluded.

2.3. Study Protocol. PPCI was performed in accordance with the protocol of the study hospital [12–14]. A transradial artery approach using 6F Kimny guiding catheter (Boston Scientific, One Scimed Place, Maple Grove, MN, USA) was utilized for both coronary arterial occlusion diagnosis and PPCI. Intra-aortic balloon pump (IABP) support was performed through the femoral artery in patients experiencing acute pulmonary edema associated with unstable condition or hemodynamic instability. Patients whose systolic blood pressure could not be maintained above 75 mmHg after IABP support and intravenous administration of more than 20 μg/kg/min dopamine were treated with extracorporeal membrane oxygenation (ECMO). All patients received dual antiplatelet therapy with a loading dose of clopidogrel (600 mg) or ticagrelor (180 mg), each combined with aspirin (300 mg), in the emergency department, followed by treatment with a maintenance dose of the same medications. The dual antiplatelet therapy was discontinued in cases where patients experienced major bleeding. The outcomes of patients who received PPCI with door-to-balloon time of <60 min (<60 group) were compared with those of patients who received PPCI with door-to-balloon time between 60 and 90 min (60–90 group).

2.4. Measures. The patient demographic and clinical information was obtained from the ED administrative database. The outcome indicators after PPCI included the left ventricular (LV) function and rates of the final thrombolysis in myocardial infarction (TIMI) 3 blood flow in the infarct-related artery, 30-day recurrent myocardial infarction (MI), and 30-day mortality. The LV function was assessed using transthoracic echocardiography. Additionally, the internal LV dimensions (i.e., end-systolic diameter [ESD] and end-diastolic diameter [EDD]) were measured based on the American Society of Echocardiography's leading-edge method using at least three consecutive cardiac cycles with the patients in the supine position. The LV ejection fraction (LVEF) was calculated as follows: LVEF (%) = $[(\text{LV EDD}^3 - \text{LV ESD}^3)/\text{LV EDD}^3] \times 100\%$.

2.5. Statistics. For continuous variables, the data were summarized as the mean and standard deviation (SD) and analyzed using Student's t-test. Categorical variables were summarized as numbers and percentages, and the chi-square test was used to evaluate the associations between the outcome groups. In the multivariate analyses, binary logistic regression models were applied to assess the effect of <60 min door-to-balloon time on documented patient outcomes to adjust for the potential confounding factors. The effects were estimated in terms of adjusted odds ratios (aORs) and the corresponding 95% confidence intervals (CIs). The results were considered statistically significant if a p value < 0.05 was obtained (two-tailed Student's t-test). The statistical analysis was performed using SPSS for Windows version 12.0 (SPSS, Chicago, IL, USA).

3. Results

3.1. Patient Demographics. During the study period, the data of 345 adult patients with STEMI visiting the ED were analyzed. A total of 241 (69.9%) and 104 patients (30.1%) received PPCI with door-to-balloon times <60 min and between 60 and 90 min, respectively. Table 1 shows the baseline demographics and clinical histories of the two study groups. The baseline demographics were comparable between the two study groups.

3.2. Event and Procedural Characteristics. Table 2 presents the event and procedural characteristics. In the <60 group, the time from patient registration to electrocardiography examination and the time of a catheter guidewire crossing the culprit lesion in the cardiac catheterization laboratory were 3.8 and 48.4 min, respectively. In the 60–90 group, the corresponding values were 9.8 and 72.2 min, respectively. The drug selection for the dual antiplatelet therapy was similar in the two study groups. Twenty-four patients stopped receiving aspirin treatment due to bleeding (14 [5.8%] and 10 [9.6%] patients in the <60 and 60–90 groups, resp., [$p = 0.202$]). More patients presented with Killip class III or IV MI and received cardiopulmonary resuscitation, endotracheal intubation, and IABP in the 60–90 group compared to the <60 group. The differences in the incidence of pulseless ventricular tachycardia, ventricular fibrillation,

Table 1: Baseline demographic and clinical history.

Variables	Door-to-balloon < 60 min (n = 241)	Door-to-balloon 60~90 min (n = 104)	p value
Age (years)	59.0 ± 12.04	62.6 ± 12.06	0.012
Male	213 (88.4%)	90 (86.5%)	0.631
Body mass index (kg/m^2)	25.5 ± 3.68	25.0 ± 4.19	0.303
Mean artery pressure (mmHg)	105.0 ± 26.87	101.6 ± 24.24	0.278
Diabetes	73 (30.3%)	36 (34.6%)	0.428
Hypertension	152 (63.1%)	68 (65.4%)	0.682
Hyperlipidemia	139 (57.7%)	56 (53.8%)	0.510
Smoking	122 (50.6%)	42 (40.4%)	0.081
Previous myocardial infarction	21 (8.7%)	14 (13.5%)	0.180
History of PCI*	21 (8.7%)	14 (13.5%)	0.180

*PCI: percutaneous coronary intervention.

Table 2: Event and procedural characteristics.

Variables	Door-to-balloon < 60 min (n = 241)	Door-to-balloon 60~90 min (n = 104)	p value
Door-to-ECG time	3.8 ± 4.95	9.8 ± 9.81	<0.001
Door-to-balloon time	48.4 ± 7.99	72.2 ± 14.09	<0.001
Dual antiplatelet therapy			
Clopidogrel and aspirin	180 (74.7%)	79 (76.0%)	0.802
Ticagrelor and aspirin	61 (25.3%)	25 (24.0%)	
Killip III-IV	50 (20.7%)	33 (31.7%)	0.029
Pulseless VT/Vf*1	20 (8.3%)	14 (13.5%)	0.140
AV conduction block*2	17 (7.1%)	12 (11.5%)	0.168
Cardiopulmonary resuscitation	11 (4.6%)	13 (12.5%)	0.008
Endotracheal intubation	16 (6.6%)	20 (19.2%)	<0.001
Intra-aortic balloon pumping	33 (13.7%)	24 (23.1%)	0.031
Extracorporeal membrane oxygenation	6 (2.5%)	5 (4.8%)	0.261
Occlusion vessel number			
One	120 (49.8%)	47 (45.2%)	0.735
Two	55 (22.8%)	26 (25.0%)	
Three	66 (27.4%)	31 (29.8%)	

*1 Pulseless VT/Vf: pulseless ventricular tachycardia/ventricular fibrillation.
*2 AV conduction block: atrioventricular conduction block.

and atrioventricular conduction block and ECMO use were not statistically significant between the two study groups. The numbers of occluded vessels in the two groups were also similar (Table 2).

3.3. Outcome. Overall, the LVEF was 57.1%, the final TIMI flow < 3 incidence in the infarct-related artery was 12.2%, and the 30-day recurrent MI and 30-day mortality rates were 4.1% and 4.9%, respectively. A stratified analysis was conducted considering the difference in Killip class distribution in the two study groups. No statistical difference in the LV function was found in the subgroup analysis. The mean LVEFs of Killip classes I and II patients with door-to-balloon times of <60 and 60–90 min were 58.8% and 57.8% ($p = 0.631$), respectively. Additionally, those of Killip classes III and IV patients with door-to-balloon times of <60 and 60–90 min were 53.4% and 51.0% ($p = 0.400$), respectively. However, in patients with Killip classes I and II MI (Figure 1(a)), those with <60 min door-to-balloon time had better blood flow in the infarct-related artery (9.2% fewer patients with TIMI flow < 3, $p = 0.019$) and 8.0% lower 30-day mortality rate ($p < 0.001$) than those with 60–90 min door-to-balloon time. No statistical significance was observed in patients with Killip classes III and IV MI (Figure 1(b)), although the

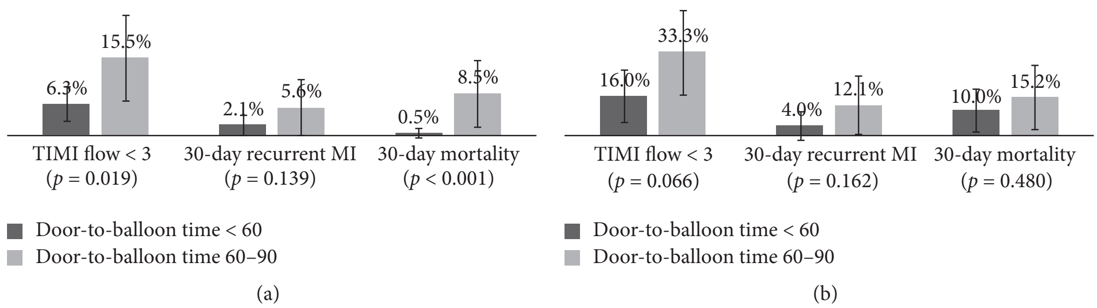

Figure 1: The incidence of TIMI flow < 3, 30-day recurrent MI, and 30-day mortality of patients with door-to-balloon time < 60 min and 60–90 min in Killip I and II (Figure 1(a)) and Killip III and IV (Figure 1(b)).

Table 3: The association between door-to-balloon time less than 60 minutes and patient outcome by logistic regression analysis.

Outcome	Door-to-balloon < 60 min		Door-to-balloon 60~90 min
	aOR	95% CI	Reference
TIMI flow < 3*	0.4	0.20~0.76	1
30-day reinfarction	0.3	0.10~0.91	1
30-day mortality	0.3	0.09~0.77	1

*TIMI flow < 3: thrombolysis in myocardial infarction (TIMI) flow < 3. aOR: adjusted odds ratio, adjusted for the potential confounding factors including age, sex, and Killip class. 95% CI: 95% confidence interval.

<60 group seemed to have better outcomes than the 60–90 group. A logistic regression model analysis was conducted to simultaneously control the potential confounding factors, including age, sex, and Killip class. Patients with <60 min door-to-balloon time had lower incidence of TIMI flow < 3 (aOR = 0.4, 95% CI = 0.20–0.76) and rates of 30-day recurrent MI (aOR = 0.3, 95% CI = 0.10–0.91) and 30-day mortality (aOR = 0.3, 95% CI = 0.09–0.77) than those with 60–90 min door-to-balloon time (Table 3).

4. Discussion

The effect of the <60 min door-to-balloon time on the outcomes of STEMI patients has not been widely studied. One study demonstrated that the prevalence of the final TIMI flow < 3, advanced congestive heart failure, and 30-day mortality did not differ between patients with <60 min door-to-balloon time and those with >60 min door-to-balloon time [15]. This finding might be attributed to the inclusion of referral patients in the study. Thus, the treatment time may have been influenced by the transfer interval. Wang et al. (2016) reported that ≤60 min door-to-balloon time was associated with better survival rates in younger STEMI patients undergoing PPCI than in elderly patients [10]. However, this study excluded patients undergoing PPCI with >90 min door-to-balloon time. After exclusion of patients with >90 min door-to-balloon time, who might potentially have worse prognosis, our study demonstrated that the shortening of door-to-balloon time to <60 min could improve the postprocedural TIMI flow and lower the 30-day recurrent infarction and 30-day mortality rates.

The results of our study demonstrate that the most important effect of shortening the door-to-balloon time to <60 min was the lowered 30-day mortality rate. The overall mortality rate was 4.9%, which was slightly higher than the data reported by Menees et al. (2013) (3.8%) [8]. We believe that this finding might be caused by the differences in disease severity distribution. Following the stratification of the analysis, we found that the subgroup with Killip classes I and II MI showed a major difference in mortality rate, which was 8% lower in patients with <60 min door-to-balloon time than in those with 60–90 min door-to-balloon time. In fact, in patients with Killip classes III and IV MI, those with <60 min door-to-balloon time displayed 5.2% lower mortality rate than those with 60–90 min door-to-balloon time, although the difference was not statistically significant. We found that door-to-balloon time of <60 min still played an important role in patient mortality rate reduction even after controlling the potential confounding factors, including age, sex, and Killip class, using a regression model. Therefore, the decreased time interval used may have been insufficient in the recent studies reporting that further shortening of the door-to-balloon time might not improve the patient mortality rate [7, 8]. We believe that the shortening of door-to-balloon time to <60 min could improve STEMI mortality rate by excluding referral patients and controlling for disease severity.

Some studies have reported healthcare system issues and patient demographic characteristics as predictors of door-to-balloon time delay, including the need for hospital transfer, nondaytime presentation, low-volume medical units, older age, female sex, and race [16, 17]. Swaminathan et al. (2013) have highlighted some clinical issues as predictors of door-to-balloon time delay, including resuscitation for cardiac arrest, intubation for respiratory failure, difficulty in obtaining vascular access and crossing the culprit lesion, and providing consent [18], as we did in our study. More patients received cardiopulmonary resuscitation, intubation, and IABP in the 60–90 group compared to the <60 group. Interestingly, the door-to-ECG time was 6 min shorter in the <60 group than in the 60–90 group. The shortening of door-to-ECG time might be an important strategy to reduce the door-to-balloon time. ECG is a key step for STEMI diagnosis. However, one challenge in the diagnosis is that one-third of patients with MI do not experience chest pain [19] and thus are given a low acuity triage score when they present at an ED, which is associated with ECG and treatment delays [20, 21]. Such patients have increased morbidity and mortality compared with those who present with chest pain [19, 22]. One solution for this problem might be the establishment of a chief complaint-based cardiac triage protocol to streamline ECG completion and shorten the door-to-ECG time [23].

5. Conclusion

Our study demonstrated that <60 min door-to-balloon time is associated with better blood flow in the infarct-related artery and lower 30-day recurrent MI and 30-day mortality rates.

Additional Points

Several limitations exist in this study. First, this is a single-center study with a relatively smaller sample size. Second, some confounding factors may still not be accounted for due to the retrospective nature of the study. Third, the symptom-to-balloon time is not included in the analysis of this study, which might also influence the result. Fourth, this study did not trace the patients' long-term outcomes; thus, the long-term mortality rate or quality of life was not discussed.

Conflicts of Interest

There are no conflicts of interest regarding the publication of this article.

Acknowledgments

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Research Article

Hemodynamic Analysis of Pediatric Septic Shock and Cardiogenic Shock Using Transpulmonary Thermodilution

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Septic shock and cardiogenic shock are the two most common types of shock in children admitted to pediatric intensive care units (PICUs). The aim of the study was to investigate which hemodynamic variables were associated with mortality in children with shock. We retrospectively analyzed 50 children with shock (37 septic shock cases and 13 cardiogenic shock cases) in the PICU and monitored their hemodynamics using transpulmonary thermodilution from 2003 to 2016. Clinical factors were analyzed between the patients with septic and cardiogenic shock. In addition, hemodynamic parameters associated with mortality were analyzed. The 28-day mortality was significantly higher in the septic group than in the cardiogenic group ($p = 0.016$). Initially, the parameters of cardiac output and cardiac contractility were higher in the septic group ($p < 0.05$) while the parameters of preload and afterload were all higher in the cardiogenic group ($p < 0.05$). Cardiac index was significantly lower in the nonsurvivors of cardiogenic shock at the time of initial admission and after the first 24 hours (both $p < 0.05$), while systemic vascular resistance index (SVRI) was significantly lower in the nonsurvivors of septic shock ($p < 0.001$). Therefore, during the first 24 hours after intensive care, SVRI and cardiac index are the most important hemodynamic parameters associated with mortality.

1. Introduction

Circulatory shock causes mortality in children and accounts for one-third of cases in intensive care units (ICUs) [1, 2]. Septic shock and cardiogenic shock are the two most common types accounting for three-fifth and one-fifth of the shock population, respectively, in ICUs [1, 2]. Some studies reported that the mortality rate was ~40 to 80% in septic shock and 60% in cardiogenic shock [3, 4]. Delay in the management and recognition of potential clinical symptoms/signs of compensated shock could lead to a high mortality rate [5]. Consequently, timely interventions to maintain an adequate tissue perfusion and oxygenation could significantly decrease the morbidity and mortality in children admitted to ICUs [6, 7]. Hemodynamic monitoring is essential for the diagnosis and therapeutic management of critically ill patients. Initially, physical examinations, vital signs, urine output, central venous pressure, and transthoracic echocardiography are often used to evaluate the preload and afterload status and cardiac functions in response to fluid resuscitation [8]. However, numerous studies recently demonstrated the inaccuracy of the methods of assessments for hemodynamic status compared to the objective hemodynamic parameter measurements [9–11]. Advanced hemodynamic monitoring may provide useful and precise data on preload, afterload, cardiac output (CO), cardiac contractility, and severity of pulmonary edema in patients with shock. In addition, assessing the severity of shock guided with an advanced hemodynamic monitoring may assist primary critical care physicians in treating patients and attribute a better clinical outcome.

Transpulmonary thermodilution, such as pulse index continuous CO (PiCCO), is a less invasive procedure (central venous and arterial catheters) and has been widely used in critically ill pediatric patients [12, 13]. Despite the frequent use of the PiCCO technique in pediatric patients, only few studies compared the hemodynamic parameters between the different types of shock and the chain of alternation between mortality and survival groups after treatment [14, 15]. In addition, there are insufficient data on what parameters are associated with mortality in critically ill pediatric patients. Therefore, the study aims to compare the parameters of septic and cardiogenic shock using the PiCCO system by analyzing the changes in hemodynamics in the mortality and survival groups. Moreover, we also identified the related parameters in predicting the survival and mortality in the critically ill pediatric patients with septic and cardiogenic shock.

2. Materials and Methods

2.1. Patient Population. This retrospective study of children aged 0 to 18 years presenting with shock to the pediatric ICU (PICU) was conducted in a tertiary medical center in Taiwan from 2003 to 2016. The PICU of our hospital was a tertiary ICU with 29 beds and hospitalized patients aged from 1 month to 18 years. The study criteria were uniformly applied to all patients screened in the study, making the study internally standardized based mainly on the international consensus conference, Paris, France, 2006 [16]. The types of shock categorized in mutually exclusive categories in the setting included septic and cardiogenic shock. The study was approved by the Institutional Review Board of Chang Gung Memorial Hospital.

2.2. Study Design. The critically ill children with hemodynamics monitoring via the PiCCO system (PiCCO, Pulsion Medical Systems, Munich, Germany) were included in this study. The transpulmonary thermodilution provided the following: (1) preload parameters: global end-diastolic volume index (GEDVI), intrathoracic blood volume index (ITBVI), and stroke volume variation (SVV); (2) cardiac parameters: CO, cardiac index (CI), and global ejection fraction (GEF); (3) afterload parameters: systemic vascular resistance index (SVRI); and (4) lung parameters: extravascular lung water index (EVLWI) and pulmonary vascular permeability index (PVPI). Information related to the cases of septic and cardiogenic shock included age; sex; cardiac characteristics, such as initial inotropic equivalent, heart rate (beats/min), and mean arterial pressure (MAP; mmHg); parameters of the PiCCO system; length of stay in the hospital and PICU; and mortality.

Two sets of measurements were analyzed and compared. Initial parameters were detected within 2 hours of enrollment after the PICU admission. Other data were obtained 24 hours after the critical care under the monitoring of the PiCCO system. Hemodynamic parameters were analyzed between the survivors and nonsurvivors in both the cardiogenic and septic groups. Moreover, we identified the predictors of mortality in the children with cardiogenic and septic shock. The primary outcome was the 28-day mortality rate in the PICU (death from any cause before day 28), and the secondary outcome was the ICU length of stay.

2.3. Measurement of PiCCO Parameters. Three consecutive cold boluses are required for each calibration to obtain the mean measurements [13]. Measurements were performed every 12 hours and whenever any hemodynamic deterioration developed. Data were recorded and exported to the computer using the PiCCO-VoLEF Data Acquisition software (version 6.0; Pulsion Medical Systems) combined with the PiCCO plus device (PC 8100 software version 5.1). The following formula was used:

$$\Delta \text{SVRI} = \frac{(24\text{-hour SVRI} - \text{baseline SVRI})}{\text{baseline SVRI}} \times 100. \qquad (1)$$

2.4. Statistical Analysis. The Chi-square test, Fisher's exact test, Student's t-test, Mann–Whitney U test, and multivariate logistic regression analysis were used where appropriate. In the descriptive analysis, values were presented as means ± standard deviations (SDs). The difference between the groups was presented as 95% confidence intervals (CIs). For comparison of dichotomous variables between the groups, the Chi-square test or Fisher's exact test was used. Comparisons of continuous variables between the two groups were performed using the Mann–Whitney U test. Predicted probabilities of mortality and 95% CIs were calculated using the logistic regression model, and survival was analyzed using the Kaplan-Meier curve. Finally, the receiver operating characteristic (ROC) curve was applied to determine the ideal cut-off values for the hemodynamic parameters for mortality in shock. The test characteristics of the different cut-off values, including sensitivity, specificity, area under the ROC curve (AUC), positive likelihood ratio (LR^+), and negative likelihood ratio (LR^-), were also examined.

The AUC, calculated using the trapezoidal rule, was considered a standard measure for the diagnostic value of the parameter. An optimal test result had a value of 1.0, while a useless test result had a value of 0.5. The LR^+ and LR^- were calculated for the best cut-off values. The criterion value indicated the value corresponding to the highest accuracy (minimal false negative and false positive results). Statistical significance was set at $p < 0.05$. All statistical analyses were performed using the SPSS software (version 22.0; SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Demographics of the Children Implanted with the PiCCO Device. During the 13-year study period, 52 children with septic or cardiogenic shock monitored using the PiCCO system were gathered; however, two cases were excluded owing to insufficient data. Therefore, a total of 50 children were reenrolled in our study, with 30 male (60%) and 20 female (40%) patients (Table 1). There were 37 (74%) cases of septic shock and 13 (26%) cases of cardiogenic shock. The mean age was lower in the cardiogenic group (9.1±6.1 years) than in the septic group (12.2 ± 4.5 years). The initial cardiac characteristics showed no significant difference between the two groups. However, the 28-day mortality rate was significantly higher in the septic group than in the cardiogenic group (59.5% versus 15.4%, $p = 0.016$) (Figure 1).

Table 1: Demographics of shock cases and initial PiCCO parameters.

Variables	Cardiogenic shock (n = 13)	Septic shock (n = 37)	p value
Age (years)	9.1 ± 6.1	12.2 ± 4.5	0.1
Gender			0.43
Male	9	21	
Female	4	16	
Cardiac characteristics			
inotropic equivalent	30.6 ± 30.3	46.4 ± 44.3	0.241
heart rate, beats/min	131.5 ± 33.2	138.2 ± 27.3	0.468
Mean arterial pressure, mm Hg	71.5 ± 15.1	69.4 ± 19.2	0.71
Outcomes			
Length of stay (days)	53.7 ± 85.7	34.8 ± 37.9	0.456
ICU stay (days)	28.1 ± 32.2	25.1 ± 32.4	0.779
Mortality	2	22	0.016
PiCCO parameters (Day 1)			
Cardiac output			
CO, L/min	2.68 ± 0.79	4.22 ± 1.65	<0.001
Cardiac contractility			
CI (L/min/m^2)	2.84 ± 1.02	3.75 ± 1.08	0.011
GEF (%)	17.8 ± 8	27.95 ± 9.15	0.001
CFI (l/min)	5.73 ± 2.54	9.46 ± 2.76	<0.001
Preload parameters			
GEDVI (mL/m^2)	519.11 ± 134.53	420.54 ± 118.01	0.017
ITBVI (mL/m^2)	648.38 ± 168.38	525.23 ± 147.59	0.017
SVV (%)	13.84 ± 5.49	15 ± 6.5	0.568
Afterload parameters			
SVRI (dyn$*$s$*$cm$^{-5}*$m^2)	1936.79 ± 802.41	1327.34 ± 705.48	0.013
Lung parameters			
EVLWI (mL/m^2)	18.46 ± 12.01	14.8 ± 12.19	0.359
PVPI	3.99 ± 2.79	3.88 ± 2.53	0.898

ICU = intensive care unit; CO = cardiac output; CI = cardiac index; GEF = global ejection fraction; CFI = cardiac function index; GEDVI = global end-diastolic volume index; ITBVI = intrathoracic blood volume index; SVV = stroke volume variation; SVRI = systemic vascular resistance index; EVLWI = extravascular lung water index; PVPI = pulmonary vascular permeability index.

3.2. PiCCO Parameters at the Initial Admission and 24 Hours after PICU Admission. As shown in Table 1, the PiCCO parameters of CO and cardiac contractility, such as CI, GEF, and cardiac function index (CFI), were higher in the septic group than in the cardiogenic group (all $p < 0.05$). However, the parameters of preload and afterload, including the GEDVI, ITBVI, and SVRI, were higher in the cardiogenic group than in the septic group ($p < 0.05$). The factors between the survivors and nonsurvivors in both groups were identified and are shown in Tables 2 and 3. As shown in Table 2, the MAP was significantly lower in the nonsurvivors than in the survivors in the septic group at the time of PICU admission ($p < 0.05$). However, the CO and CI were significantly lower in the nonsurvivors in the cardiogenic group initially (both $p < 0.05$). The changes in the PiCCO parameters after treatment for 24 hours are presented in Table 3. The MAP was lower in the nonsurvivors than in the survivors in the septic group ($p < 0.001$). In addition, both the CO and CI were lower in the nonsurvivors than in the survivors in the cardiogenic group (both $p < 0.05$). However, notably, the SVRI was statistically and significantly lower in the nonsurvivors than in the survivors (901.08±305.69 versus 1584.23 ± 429.63) in the septic group ($p < 0.001$).

3.3. Factors Associated with Mortality. The results of the multivariate logistic regression analysis showed that SVRI was an independent predictor of mortality after the 24-hour critical care in the PICU in the septic group (odds ratio [OR], 0.995; 95% CI, 0.992–0.998, and $p = 0.003$). Based on the ROC analysis of SVRI in predicting the survivors in the septic group, the AUC was 0.9 (95% CI, 0.786–1, $p < 0.001$) (Figure 2). The cut-off values of SVRI in the septic group are shown in Table 4. We identified SVRI of 1167 dyn$*$s$*$cm$^{-5}*$m^2 as the appropriate point to predict

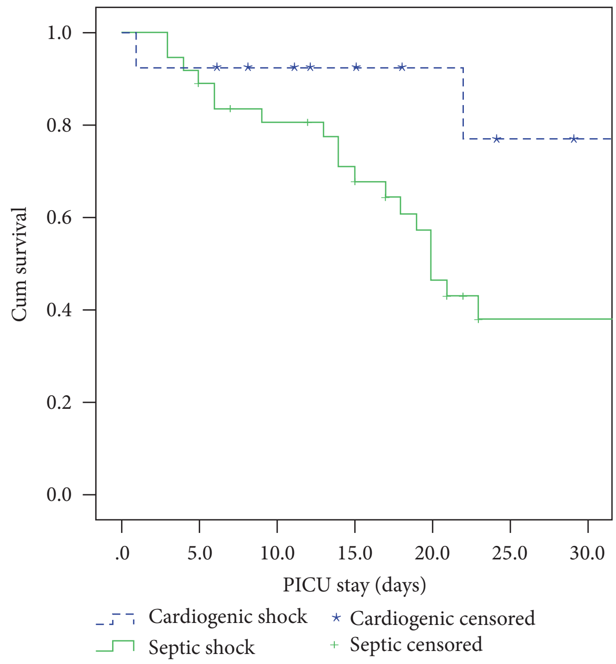

FIGURE 1: Survival rate analysis of children between septic and cardiogenic shock during the first 28 days of PICU stay ($p < 0.05$).

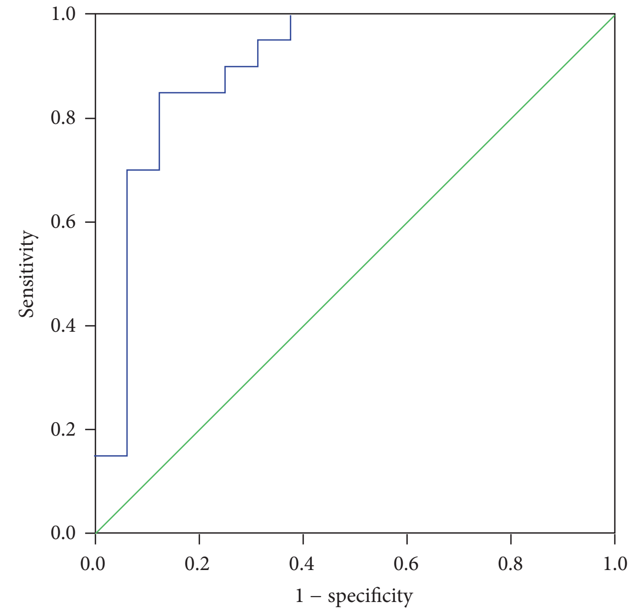

FIGURE 2: Receiver operator characteristic analysis for SVR in predicting mortality in septic shock after the 24 hours of admission to the PICU.

mortality. We also found that the change in SVRI (ΔSVRI) was negatively correlated with mortality (OR, 0.974; 95% CI, 0.952–0.997; $p = 0.027$).

4. Discussion

Shock is a major cause of morbidity and mortality in the PICU. In-hospital mortality rates of septic shock are high, ranging between 18% and 50% [1]. Mortality increases with the severity of sepsis. Hemodynamic monitoring is essential for the diagnosis and therapeutic management of critically ill patients. In the 13-year retrospective study, we found that SVRI was the most powerful predictor of the 28-day mortality in children with septic shock. There are few studies that demonstrate the importance of SVRI in adults with sepsis [17]; the present study is the first study to identify the importance of SVRI in predicting the mortality in children with septic shock. The SVRI of 1167 $dyn*s*cm^{-5}*m^2$ during the first 24 hours after intensive care was the useful predictor of the 28-day mortality. In addition, we found that the change in SVRI (ΔSVRI) correlated with mortality negatively. In our study, the decreased CI in the children was an independent risk factor for mortality in the cardiogenic group, which was consistent with those of previous studies [18, 19].

A decreased SVRI indicates the expression of injuries in the endothelial layer; endothelial injuries are one of the important pathophysiologies of sepsis [20]. In sepsis, the injured endothelial cells could increase the secretions of reactive oxidants, lytic enzymes, prostacyclin, lipopolysaccharide, vasoactive substances, such as endothelin, platelet-derived growth factor, and the most important substance-overproduction of nitric oxide (NO) [20, 21]. Increasing NO synthesis by injured endothelial cells would damage the cerebral autonomic centers, which would further reduce the vascular reactivity to vasoconstrictors, causing a refractory hypotension [22, 23]. Another important factor causing hypotension in sepsis is the decreased compensatory secretion of vasopressin, which may be caused by impairing the baroreflex-mediated secretion [24]. Therefore, hypotension due to vasodilation, especially from endothelial injuries, may be the critical cause of circulatory malfunction in sepsis.

Although vasodilation induced by endothelial injuries may be the predictor of mortality in septic patients reported in some studies [20], the clinical application of SVRI has not been established in children. We estimated the association between the hemodynamic variables and clinical outcomes during the first 24 hours after intensive care because the therapeutic treatment during the early phase of shock could be crucial for survival [19, 25, 26]. The study demonstrated that the decreased value of SVRI after the 24-hour intensive care may serve as the early predictor of prognosis in children with sepsis, which is consistent with the results of a previous study in adults [17]. Several studies reported that the severity of pulmonary edema evaluated using the EVLWI and PVPI was the independent risk factor for mortality in sepsis [15, 18, 27]. However, although the nonsurvivors in our study had higher EVLWI and PVPI levels than that of the survivors, no significant difference was noted in the first 24 hours after the treatment. The difference may be that other studies analyzed the EVLWI at the maximum value and often developed 72 hours after intensive care, which is compatible with the clinical course of severe pulmonary edema commonly developing after 72 hours of intensive care [18, 27, 28].

On the other hand, CI was the independent risk factor for mortality in the pediatric cardiogenic shock in our study,

Table 2: Initial PiCCO parameters between survivors and nonsurvivors in children with cardiogenic shock and septic shock at the time of admission to the PICU.

Characteristics	Cardiogenic Shock			Septic shock		
	Death ($n = 3$)	Survival ($n = 11$)	p value	Death ($n = 22$)	Survival ($n = 15$)	p value
Age (years)	8.7 ± 10.89	9.15 ± 5.69	0.927	12.62 ± 4.3	11.53 ± 4.81	0.476
Gender			0.522			0.729
Male	1	8		13	8	
Female	1	3		9	7	
LOS in ICU	11.5 ± 14.85	31.01 ± 34.04	0.453	24.05 ± 38.43	26.73 ± 22.02	0.808
Cardiac characteristics						
inotropic equivalent	63.75 ± 76.91	24.55 ± 17.04	0.598	56.11 ± 54.33	32.17 ± 15.93	0.107
heart rate (beats/min)	121.75 ± 32.17	132.23 ± 34.63	0.673	137.83 ± 28.51	138.94 ± 26.38	0.906
Mean arterial pressure (mm Hg)	67.34 ± 26.4	72.3 ± 14.09	0.687	64.24 ± 17.73	76.87 ± 19.4	0.048
PiCCO parameters						
Cardiac output						
CO (L/min)	1.6 ± 0.06	2.88 ± 0.69	0.028	4.31 ± 1.59	4.09 ± 1.76	0.705
Cardiac contractility						
CI (L/min/m^2)	1.34 ± 0.09	2.93 ± 0.98	0.049	3.68 ± 0.93	3.86 ± 1.29	0.626
GEF (%)	15.25 ± 4.59	18.27 ± 8.55	0.645	27.49 ± 10.26	28.56 ± 7.72	0.739
CFI (l/min)	4.48 ± 2.93	5.91 ± 2.58	0.584	9.01 ± 2.59	10.08 ± 2.95	0.263
Preload parameters						
GEDVI (mL/m^2)	458.75 ± 51.97	530.08 ± 143.48	0.514	424.52 ± 107.12	415.23 ± 134.88	0.822
ITBVI (mL/m^2)	572.41 ± 65.17	662.19 ± 179.54	0.512	530.18 ± 134.03	518.64 ± 168.63	0.823
SVV (%)	12.58 ± 0.12	14.07 ± 5.98	0.741	15.54 ± 7.23	14.21 ± 5.39	0.55
Afterload parameters						
SVRI, dyn$*$s$*$cm$^{-5}*$m^2	1794.4 ± 219.08	1962.67 ± 873.53	0.798	1196.75 ± 509.52	1510.17 ± 901.11	0.193
Lung parameters						
EVLWI, mL/m^2	18.16 ± 3.06	18.52 ± 13.18	0.97	15.34 ± 13.51	14.09 ± 10.58	0.769
PVPI	4.02 ± 2	3.98 ± 2.99	0.99	3.99 ± 2.84	3.74 ± 2.12	0.774

ICU = intensive care unit; CO = cardiac output; CI = cardiac index; GEF = global ejection fraction; CFI = cardiac function index; GEDVI = global end-diastolic volume index; ITBVI = intrathoracic blood volume index; SVV = stroke volume variation; SVRI = systemic vascular resistance index; EVLWI = extravascular lung water index; PVPI = pulmonary vascular permeability index.

and the results were consistent with those of previous studies in adults [19, 26, 29]. According to the pathophysiology, CI may be related to the base deficit. Our study observed that a decreased CI in the first 24 hours after intensive care could reflect the failure of hemodynamic interventions in nonsurvivors. Although only two nonsurvivors were included in our analysis, both cases had the lowest CIs among the cases of cardiogenic shock.

In conclusion, SVRI and CI are the most important hemodynamic parameters associated with the 28-day mortality in children with septic shock and cardiogenic shock, respectively, during the first 24 hours after intensive care. Most importantly, we determined the SVRI of 1167 dyn$*$s $*$cm$^{-5}*$m^2 as the best appropriate predictor of mortality after 24-hour intensive care interventions.

Abbreviations

PICU: Pediatric intensive care unit
PiCCO: Pulse index continuous cardiac output
GEDVI: Global end-diastolic volume index
ITBVI: Intrathoracic blood volume index
SVV: Stroke volume variation
CO: Cardiac output
CI: Cardiac index
GEF: Global ejection fraction
SVRI: Systemic vascular resistance index
EVLWI: Extravascular lung water index
PVPI: Pulmonary vascular permeability index
LOS: Length of stay
SD: Standard deviation
CIs: Confidence intervals.

Ethical Approval

The study protocol was approved by the Institution Review Board and ethics committee of Chang Gung Memorial hospital.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Table 3: The PiCCO parameters between survivors and nonsurvivors after 24 hours of setting up the PiCCO.

Variables	Cardiogenic shock			Septic shock		
	Death ($n = 3$)	Survival ($n = 11$)	p value	Death ($n = 22$)	Survival ($n = 15$)	p value
Cardiac characteristics						
heart rate (beats/min)	120 ± 33.9	137.3 ± 39.2	0.572	139.18 ± 26.26	125.64 ± 32.45	0.169
Mean arterial pressure (mm Hg)	68.5 ± 23.3	79.9 ± 12	0.292	59.8 ± 14.84	84.13 ± 19.19	<0.001
PiCCO parameters						
Cardiac output						
CO (L/min)	1.53 ± 0.01	3.57 ± 0.97	< 0.001	5.01 ± 1.59	3.99 ± 1.55	0.062
Cardiac contractility						
CI (L/min/m^2)	1.33 ± 0.11	3.59 ± 1.32	0.039	4.23 ± 0.92	3.77 ± 1.01	0.166
GEF (%)	15 ± 4.24	19.4 ± 7.56	0.451	30.93 ± 11.29	30.02 ± 11.46	0.812
CFI (l/min)	4.65 ± 2.76	6.56 ± 2.45	0.336	9.69 ± 3.34	9.09 ± 2.92	0.574
Preload parameters						
GEDVI (mL/m^2)	452.5 ± 47.38	572.06 ± 106.39	0.157	457.82 ± 140.55	449.44 ± 156.64	0.867
ITBVI (mL/m^2)	565 ± 59.39	714.82 ± 132.98	0.156	571.84 ± 175.74	561.3 ± 195.83	0.866
SVV (%)	11.25 ± 3.18	13.48 ± 5.72	0.61	15 ± 5.97	11.3 ± 5.87	0.068
Afterload parameters						
SVRI, ($dyn*s*cm^{-5}*m^2$)	1742 ± 270.11	1664.48 ± 469.75	0.829	901.08 ± 305.69	1584.23 ± 429.63	<0.001
Lung parameters						
EVLWI (mL/m^2)	16.5 ± 2.12	17 ± 11.63	0.954	16.5 ± 13.85	11.88 ± 6.53	0.229
PVPI	3.65 ± 1.63	3.06 ± 1.52	0.626	4.07 ± 2.8	3.09 ± 1.36	0.212

ICU = intensive care unit; CO = cardiac output; CI = cardiac index; GEF = global ejection fraction; CFI = cardiac function index; GEDVI = global end-diastolic volume index; ITBVI = intrathoracic blood volume index; SVV = stroke volume variation; SVRI = systemic vascular resistance index; EVLWI = extravascular lung water index; PVPI = pulmonary vascular permeability index.

Table 4: Predictive power of SVRI for different cut-off points in noncardiogenic group.

SVRI value	Sensitivity	Specificity	LR^+	LR^-	Youden index
533	0.15	1.0	—	0.85	0.15
591	0.15	0.938	2.4	0.907	0.0875
1093	0.7	0.937	11.2	0.32	0.6375
1115	0.7	0.875	5.6	0.347	0.575
1167*	0.85	0.875	6.8	0.171	0.725
1351	0.85	0.75	3.4	0.2	0.6
1362	0.9	0.75	3.6	0.133	0.65
1371	0.9	0.687	2.88	0.145	0.5875
1394	0.95	0.687	3.04	0.073	0.6375
1460	0.95	0.625	2.533	0.08	0.575
1531	1.0	0.625	2.667	0	0.625

LR^+: likelihood ratio for a positive test; LR^-: likelihood ratio for a negative test;
*: best cut-off point.

Authors' Contributions

En-Pei Lee and Shao-Hsuan Hsia contributed equally to the study. Shao-Hsuan Hsia and Jainn-Jim Lin participated in data analysis. Oi-Wa Chan and Chia-Ying Lin gathered the data. En-Pei Lee, Shao-Hsuan Hsia, Jung Lee, and Han-Ping Wu drafted the manuscript, with all authors revising it critically for intellectual content. All authors have read and approved the final version of this manuscript. En-Pei Lee and Shao-Hsuan Hsia contributed equally to this work.

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Research Article

Public Knowledge and Attitudes towards Bystander Cardiopulmonary Resuscitation in China

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The rate of bystander CPR is much lower in China than in developed countries. This survey was implemented to assess the current status of layperson CPR training, to analyze the willingness of bystanders to perform CPR, and to identify barriers to improving bystander CPR rates. The questionnaire included individual information, current status of bystander CPR training, and individual's willingness and attitude towards performing CPR. There were 25.6% laypersons who took CPR training. The majority (98.6%) of laypersons would perform CPR on their family members, but fewer laypersons (76.3%) were willing to perform CPR on strangers. Most respondents (53.2%) were worried about legal issues. If laws were implemented to protect bystanders who give aid, the number of laypersons who were not willing to perform CPR on strangers dropped from 23.7% to 2.4%. An increasing number of people in China know CPR compared with the situation in the past. CPR training in China is much less common than in many developed countries. The barriers are that laypersons are not well-trained and they fear being prosecuted for unsuccessful CPR. More accredited CPR training courses are needed in China. The laws should be passed to protect bystanders who provide assistance.

1. Introduction

Cardiac arrest is a substantial public health problem. Data from previous studies suggest that more than 3 million sudden cardiac deaths occur worldwide every year [1, 2], and survival is lower than 8% [3]. Unfortunately, 544,000 sudden cardiac deaths occur in China each year with survival of less than 1% [4]. Survival from sudden cardiac arrest in China is much lower than in many countries. Immediate bystander cardiopulmonary resuscitation (CPR) increases out-of-hospital cardiac arrest (OHCA) survival by twofold to threefold [5–7]. The chance of surviving OHCA falls by 7%–10% per minute without intervention [8].

The proportion and intensity of bystander CPR training vary in different countries. The main reason of the difference on bystander CPR training between countries is because of the various education and training system, such as CPR training as a part of the middle school curriculum and driver's license acquisition [9–11]. The willingness of the laypersons in different countries to learn and perform CPR is also very important. No time and no interest to learn CPR, afraid of doing something wrong, a fear of legal liability, and other reasons are obstacles limiting bystander to learn and perform CPR [12–14]. More than half of the students in the United States learned CPR and automated external defibrillator [15]. In Norway, 89% secondary school students attended CPR training [12]. Seventy percent of people in Japan learned CPR, and 30% of people learned CPR more than two times [10]. However, CPR training among Chinese students is 27%, which was much lower than in developed countries [10, 12, 15, 16].

One or two decades ago, there were few CPR training for the public and students in China. Accredited CPR training courses were only for medical staff or emergency medical service related professions, such as firefighter. With the development of China and the improvement of civilization of Chinese society, CPR training courses by medical organization, television, Internet, newspaper, and other channels are developing recent years for the public and university students, but it is still not systematic. Because of the big population of Chinese people, organized training by government such as including the training as a part of senior school curriculum

Table 1: Characteristics of the respondents.

	All	Medical related person	Layperson
Respondents	2094 (100.0%)	253 (12.1%)	1841 (87.9%)
Gender			
Male	1005 (48.0%)	100 (39.5%)	905 (49.2%)
Female	1089 (52.0%)	153 (60.5%)	936 (50.8%)
Age, y			
<18	3 (0.1%)	0 (0%)	3 (0.2%)
18–25	494 (23.6%)	51 (20.2%)	443 (24.1%)
26–45	1500 (71.6%)	196 (77.5%)	1304 (70.8%)
46–60	93 (4.4%)	6 (2.4%)	87 (4.7%)
>60	4 (0.2%)	0 (0%)	4 (0.2%)
Education level			
<associate's degree	76 (3.6%)	3 (1.2%)	73 (4.0%)
Associate's degree	359 (17.1%)	37 (14.6%)	322 (17.5%)
Bachelor's degree or above	1659 (79.2%)	213 (84.2%)	1446 (78.5%)

and driver's license acquisition is needed to be established. Also, it is important to increase the willingness of the people to supply help to cardiac arrest victims. Several surveys were conducted to investigate the knowledge and attitudes of bystander CPR on Chinese students [16, 17]. However, few studies about bystander CPR towards the public were done in China. This survey was implemented to assess current status and effects of bystander CPR training on the public, to explore the willingness of bystanders to perform CPR, and to identify barriers to improve bystander CPR rate in China.

2. Methods

This study was approved by the ethics committee of the Third Affiliated Hospital, Harbin Medical University. The data of this survey was acquired by questionnaires distributed to the public of China through the Internet.

2.1. Questionnaire Design and Distributing. The questionnaire consisted of three sections with a total of 19 questions including individual information, current status and effects of CPR training, attitude on CPR training, and willingness to providing help in emergency situation. The questionnaires were released at https://www.sojump.com from May 9 to 19, 2014. This website is one of the largest websites which provide a platform for researchers who design and release questionnaires to make all kinds of survey on the public of China. The website has over 2.6 million volunteer members in China. The questionnaires were distributed randomly to volunteer members by email invitation. There was no conflict of interest between the volunteer members and the survey. The website automatically screened IP addresses to ensure that the questionnaire was answered only once from each IP address. The website automatically ruled out answers if the feedback for the whole questionnaire was less than 2 minutes or more than 30 minutes. The time limitations are calculated automatically by the website of https://www.sojump.com according to the number and content of the questions of the questionnaire. The website provided the email address and IP address of each returned questionnaire to make sure each answered questionnaire had a reachable respondent and was credible.

2.2. Data Analysis. Percentages were calculated for the frequencies. The difference between groups was analyzed with Chi-square tests or Fisher exact tests. P values < 0.05 were considered significantly different. All statistics were processed with SPSS for Windows 17.0 (SPSS Inc., Chicago, IL, USA).

3. Results

A total of 2102 answered questionnaires were collected by May 19, 2014. Eight questionnaires were ruled out because of obvious contradictive answers. Among the valid respondents (Table 1), 87.9% were laypersons (compared with medical related person). The questionnaires answered by laypersons (1841) were selected for final analysis in this study.

3.1. Individual Information. Among the layperson respondents, 49.2% were male and 50.8% were female, 99.6% were between 18 and 60 years old, and 78.5% had a bachelor's degree or above, 17.5% had associate's degree, and 4.0% had educational level of lower than associate's degree.

3.2. Current Status and Effects of CPR Training. Among the layperson respondents, 90.1% understood what is CPR and 25.6% were trained by CPR courses (Table 2). However, among the trained laypersons, 50.8% knew the standard CPR procedure and believed they had the ability to perform CPR, and 49.2% knew the procedure only but they did not believe they had the ability to perform CPR on victims (Table 3). The top three reasons for not attending CPR training courses were not knowing where to take the training (54.7%), a lack of time

Table 2: Current status and attitude of layperson towards CPR training.

Layperson responses	All	Male	Female	P value
Understanding what is CPR				0.645
Yes	1658 (90.1%)	818 (90.4%)	840 (89.7%)	
No	183 (9.9%)	87 (9.6%)	96 (10.3%)	
CPR training				0.110
Yes	472 (25.6%)	247 (27.3%)	225 (24.0%)	
No	1369 (74.4%)	658 (72.7%)	711 (76.0%)	
Reasons for not attending CPR training				0.044
Do not know where the training is	749 (54.7%)	352 (53.5%)	397 (55.8%)	
Lack of time	275 (20.1%)	148 (22.5%)	127 (17.9%)	
Not concerned	147 (10.7%)	74 (11.2%)	73 (10.3%)	
Costs	118 (8.6%)	56 (8.5%)	62 (8.7%)	
Others	80 (5.8%)	28 (4.3%)	52 (7.3%)	
The way to learn CPR				<0.001
Teaching by medical staff	826 (44.9%)	414 (45.7%)	412 (44.0%)	
Accredited CPR training courses	511 (27.7%)	210 (23.2%)	301 (32.2%)	
TV or internet	290 (15.8%)	164 (18.1%)	126 (13.5%)	
Health education lectures	161 (8.7%)	91 (10.1%)	70 (7.5%)	
Books, newspapers, and magazines	35 (1.9%)	16 (1.8%)	19 (2.0%)	
Others	18 (1%)	10 (1.1%)	8 (0.9%)	
Do you want to pay for the qualified and professional CPR training				0.007
Yes	1032 (56.1%)	534 (59.0%)	498 (53.2%)	
No	258 (14.0%)	131 (14.5%)	127 (13.6%)	
Uncertain	551 (29.9%)	240 (26.5%)	311 (33.2%)	
Do you believe you have ability to learn and perform CPR				<0.001
Yes	1217 (66.1%)	627 (69.3%)	590 (63.0%)	
No	151 (8.20%)	83 (9.2%)	68 (7.3%)	
Uncertain	473 (25.7%)	195 (21.5%)	278 (29.7%)	
Do you believe a lifeless person without breath and/or heartbeat can be saved				<0.001
Yes	1456 (79.1%)	738 (81.5%)	718 (76.7%)	
No	61 (3.3%)	38 (4.2%)	23 (2.5%)	
Uncertain	324 (17.6%)	129 (14.3%)	195 (20.8%)	
Top 5 professions to learn CPR				0.278
Medical staff	1786 (97.0%)	873 (96.5%)	913 (97.6%)	
Firefighter	1578 (85.7%)	785 (86.7%)	793 (84.7%)	
Police officer	1396 (75.8%)	708 (78.2%)	688 (73.5%)	
Driver and steward	1217 (66.1%)	578 (63.9%)	639 (68.3%)	
Tour guide	913 (49.6%)	426 (47.1%)	487 (52.0%)	

$P < 0.05$, statistically significant difference between genders for each question.

Table 3: The effects of layperson CPR training.

Layperson responses	All	Male	Female	P value
Trained				0.469
Know procedure and can perform CPR	239 (13.0%)	129 (14.3%)	110 (11.8%)	
Know the procedure but cannot perform CPR	233 (12.6%)	118 (13.0%)	115 (12.3%)	
Not trained				0.939
Know the procedure	322 (17.5%)	152 (16.8%)	170 (18.2%)	
Know a little	733 (39.8%)	354 (39.1%)	379 (40.5%)	
Unknown	314 (17.1%)	152 (16.8%)	162 (17.3%)	

P value, compared between genders for each question.

Table 4: Layperson responses to the hypothetical cardiac arrest scenarios.

Layperson responses	All	Male	Female	P value
If you find someone who has cardiac arrest, you will				0.002
Ask for help and perform CPR	1096 (59.5%)	562 (62.1%)	534 (57.1%)	
Ask for help only	420 (22.8%)	174 (19.2%)	246 (26.3%)	
Perform CPR only	274 (14.9%)	149 (16.5)	125 (13.4)	
Do not know how to do	48 (2.6%)	19 (2.1%)	29 (3.1%)	
Others	3 (0.2%)	1 (0.1%)	2 (0.2%)	
If you experience cardiac arrest in public area, the person you wish to perform CPR on you				0.806
Bystander	994 (54.0%)	486 (53.7%)	508 (54.3%)	
Medical staff or trained people only	847 (46.0%)	419 (46.3%)	428 (45.7%)	
When you witness a family member/stranger confronting cardiac arrest, you will perform CPR to				0.094
Both of them	1395 (75.8%)	696 (76.9%)	699 (74.7%)	
Family member only	421 (22.9%)	192 (21.2%)	229 (24.5%)	
Stranger only	10 (0.5%)	6 (0.7%)	4 (0.4%)	
Neither	15 (0.8%)	11 (1.2%)	4 (0.4%)	
While performing CPR on a stranger, you will worry about				<0.001
Legal issues	980 (53.2%)	537 (59.3%)	443 (47.3%)	
Inadequate knowledge and skill of CPR	817 (44.4%)	344 (38.0%)	473 (50.5%)	
Disease transmission	33 (1.8%)	18 (2.0%)	15 (1.6%)	
Others	11 (0.6%)	6 (0.7%)	5 (0.5%)	
If a family member has cardiac arrest, but bystander CPR failed, will you prosecute for liability				<0.001
Yes	252 (13.7%)	140 (15.5%)	113 (12.1%)	
No	1085 (58.9%)	560 (61.9%)	525 (56.1%)	
Uncertain	503 (27.3%)	205 (22.7%)	298 (31.8%)	
If laws were implemented to prevent prosecuting for liability, will you perform CPR on strangers				0.029
Yes	1629 (88.5%)	812 (89.7%)	817 (87.3%)	
No	45 (2.4%)	26 (2.9%)	19 (2.0%)	
Uncertain	167 (9.1%)	67 (7.4%)	100 (10.7%)	

$P < 0.05$, statistically significant difference between genders for each question.

(20.1%), and a lack of concern (10.7%). Sixty-six point one percent of laypersons believed they had the ability to learn and perform CPR, and 79.1% believed that a lifeless person without breath and/or heartbeat could be saved. Female had less confidence than male ($P < 0.001$). The favorable methods for the laypersons to learn CPR were medical staff teaching (44.9%) or the qualified CPR training courses (27.8%). Fifty-six point one percent of laypersons were willing to pay for the CPR training courses.

3.3. Willingness to Perform CPR. If there was a cardiac arrest victim, 59.5% of laypersons stated that they would ask for help and perform CPR to rescue the victim simultaneously, 22.8% chose to ask for help only and wait for rescue, 14.9% chose to perform CPR only, and 2.6% did not know what to do (Table 4). In case of cardiac arrest, 54.0% of laypersons expected to be resuscitated by anybody nearby immediately and 46.0% of laypersons expected to be resuscitated by the medical staff or trained people only. The majority (98.7%) of laypersons chose to perform CPR on their family members when they were confronted with cardiac arrest. However, fewer laypersons (76.3%) were willing to perform CPR on strangers in comparison with family members. There was significant difference in the attitudes of the layperson on family members compared with strangers ($P < 0.05$). With hesitation to rescue strangers, 53.2% of the respondents were worried about legal issues, and 44.4% worried about inadequate knowledge. Interestingly, the most important thing that man worried about was legal issues (59.3%), and their second concern was inadequate knowledge and skill in performing CPR (38.0%). By contrast, woman worried more about inadequate knowledge and skill in CPR (50.5%), and their second concern was legal issues (47.3%). There was significant difference in the most concerned thing when performing CPR between man and woman ($P < 0.001$). Most people (58.9%) believed they would not prosecute bystanders for liability if bystander CPR on their family members failed, 13.7% would, and 27.3% were not sure. Woman had less willingness on prosecuting for liability on bystanders whose CPR failed compared with man ($P < 0.001$). In case laws were implemented to protect bystander who gave aid, the number of laypersons who were not willing to perform CPR on strangers dropped from 23.7% to 2.4% ($P < 0.001$).

4. Discussion

Bystander CPR is the most significant factor for OHCA survival. Bystander CPR rates are below 50% on average, and the rates vary between different countries according to reports [18–20]. Bystander CPR occurs less than 6% of OHCA in China [21]. For the purpose of improving the rate of bystander CPR and the ability of the layperson to perform CPR, this study was performed to find out the current status and effects of CPR training, to understand attitudes of layperson towards bystander CPR, and to uncover the barriers to improving bystander CPR rates in China. This study showed 90% of laypersons understood what is CPR in China. One-fourth of the laypersons were trained by different kinds of CPR courses. Thirteen percent of laypersons knew the standard CPR procedure and believe they had ability to perform CPR. The primary reason for layperson not learning CPR was that they did not know where to find a CPR training course. When confronting possible cardiac arrest victims, almost all laypersons chose to perform CPR on their family members, whereas a significantly decreased percentage of respondents chose to perform CPR on strangers. Bystander CPR provided by citizens is fundamentally based on goodwill and conscience towards strangers. The awareness should be emphasized by the appropriate education system. Furthermore, the primary reasons preventing bystanders from supplying help were inadequate knowledge and legal issues. It is important to set up more accredited CPR training courses in China. There are no laws to protect bystanders who are supplying help from being prosecuted in case CPR fails in China. If laws were implemented to protect bystanders who give aid, the number of laypersons who were not willing to perform CPR on strangers dropped 90%.

This study showed that the number of people who understood what is CPR was greatly extended than 7 years ago (90% versus 55%) [16]. However, layperson CPR training (25.6%) in China is still lower than most developed countries, such as Sweden (54.4%) [22], Slovenia (69.4%) [11], United States (54.1%) [23, 24], Australia (58%) [25], and New Zealand (76%) [26]. In Norway, basic life support (BLS) training was up to 89% among secondary school students [12]. In Japan, more than 70% people attended CPR training [10, 27]. Nevertheless, 26.8% of laypersons attended BLS training in Korea and 21% in Hong Kong, which is similar to the data in our study [13, 28].

This study showed that the primary reasons for layperson not attending the CPR training courses were "not knowing where are the CPR training courses" and "a lack of time and concern." The cost was not considered to be a major problem to learn CPR by the respondents. The reasons for not taking CPR training courses were the same as those noted in Belgium [14]. Although CPR training was very common, the same problems were also reported in Norway [12]. Slovenia has a rather high percentage of CPR-trained layperson, which is related to mandatory CPR training during driver's license acquisition [11]. Approximately 50 years ago, BLS was recommended as part of the school curriculum with compulsory resuscitation training in Norwegian schools [12]. CPR training is part of school law for high school graduation in approximately 20 states in the USA at present. In Japan, the percentage of high school students who had previous CPR training courses was 59% [10]. Only 27% of Chinese middle school students learned CPR from television and books, but not from accredited or formal CPR training courses [16]. University students in nonmedical related specialties in China were not required to take CPR theory or technique practice training [17]. These reports indicated that compulsory CPR training organized by government was recommended to be added to the educational system of middle school and college curriculum and driver's license acquisition to improve the ability of bystanders to perform CPR in China, which had been established many years ago in Norway, United State, Japan, and Slovenia who are good performers of bystander CPR.

Nearly half of the laypersons who were trained of CPR believed they knew the procedure only but could not perform CPR which suggested that the quality of CPR training was not satisfactory. Berden et al. reported that reinstruction at six-month intervals is needed to maintain adequate skills in CPR [29]. Similar situations were also reported in other surveys [10, 12, 13]. All Norwegian children went through one BLS course during middle school, but only 73% of the students could recall what they learned about BLS training after several years [12]. In Japan, approximately 30% of respondents attended CPR training more than twice, but some of them believed they had poor knowledge and lacked the ability to perform CPR [10]. CPR training was shown to play an important role in improving recognition of a patient with cardiac arrest [11]. Repeated and effective CPR training increased bystander's confidence and willingness to perform CPR [10, 13]. Multiple CPR training is needed for the public to provide high-quality CPR.

In this study, nearly all laypersons chose to perform CPR on their family member. However, significantly fewer respondents were willing to perform CPR on strangers. In this hesitancy to resuscitate strangers, legal issue was the number one concern of respondents. The second bystander's scruple was inadequate knowledge and skill in performing CPR. These findings were consistent with a survey from Taiwan in 2013 [30]. The first two concerns among the Norwegian students were little knowledge of BLS and a fear of harming the victims [12]. Poor knowledge/performance was the most important anxiety among Japanese teachers/students [10]. The most important thing that Chinese respondents worried about was legal issues, but poor knowledge was prior concern among laypersons of Norwegian. One of the major reasons of this difference was because there were laws to protect people who provide aid to victims in many countries, such as United States, Canada, and many European countries. These laws protect people who supplied help, as in the case of the "Good Samaritan" Law, which offers legal protection to people who give reasonable assistance to those who are injured or ill, encourage people to offer assistance, and reduce bystander hesitation to assist for fear of being sued or prosecuted for unintentional injury or wrongful death [31]. However, no relevant laws have been passed to protect people who provide help from prosecution because of failed resuscitation in China. A similar report was also published in Korea in 2010, showing that, among the respondents who declined to perform standard CPR, the majority of them cited a fear of legal liability before "Good Samaritan" legislation was passed by the government of Korea [13]. According to our study, if laws were implemented to protect bystanders who gave aid, more respondents were willing to provide help to strangers. Interestingly, males worried more about legal issues, while females concerned more about inadequate knowledge and skill of CPR. Furthermore, males reported significantly higher confidence than females in learning and performing CPR in our study, which was consistent with a previous report [12]. On the basis of these reports and the results of this study, the laws should be passed in China to encourage the people and protect the person who supply help to victims without any delay or hesitation.

5. Limitations

Our study has several limitations. First, this survey was released through a website to respondents who were registered volunteer members. The person who answered the questionnaire usually paid more attention to CPR. Therefore, there was a volunteer bias in this study. Second, only 2102 questionnaires were collected in this study, so the results of this survey are difficult to be generalized to the greater Chinese population. However, the volunteer people who finished the survey are from all over the country, including all ages with the ability to answer the questionnaires, and including all kinds of education levels and occupations. This study still showed very important information about the current status of bystander CPR training on Chinese average people in all ages and occupations, because previous studies on bystander CPR training in China were almost done on Chinese students. Third, most of respondents were between 18 and 60 years old and many of them had bachelor's degree or above. The education of the people who answered the questionnaire is above the average level of Chinese. These individuals might have more motivation and opportunity to learn and practice CPR. Thus, the data presented in this study might be optimal than the reality.

6. Conclusions

An increasing number of people understood what is CPR compared with the situation in the past with the rapid developing of the society of China. However, layperson CPR training and bystander CPR rate in China are still less common than in many developed countries. People are willing to learn and perform CPR to victims. The barriers are that laypersons are not well-trained and have fear of being prosecuted responsibility for unsuccessful CPR. Because repeated and effective CPR training are important to increase bystander's confidence and willingness to perform CPR, multiple CPR training is needed for the public to provide high-quality CPR. Besides, the awareness should be emphasized by the appropriate education system to motivate people to supply help in emergency situation. The laws protecting laypersons who provide reasonable aid are needed to be made to encourage people to offer assistance without any hesitation in China.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Meng Chen and Yue Wang contributed equally to this work. Meng Chen, Yue Wang, Xuan Li, Lina Hou, and Fei Han conceived and designed the experiments. Meng Chen, Yue Wang, and Xuan Li performed the experiments. Meng Chen, Yue Wang, Xuan Li, Lina Hou, Yufeng Wang, and Jie Liu analyzed the data. Meng Chen, Yue Wang, Xuan Li, and Fei Han wrote the paper. All authors read and approved the final manuscript.

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Research Article

Demographics and Clinical Features of Postresuscitation Comorbidities in Long-Term Survivors of Out-of-Hospital Cardiac Arrest: A National Follow-Up Study

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The outcome of patients suffering from out-of-hospital cardiac arrest (OHCA) is very poor, and postresuscitation comorbidities increase long-term mortality. This study aims to analyze new-onset postresuscitation comorbidities in patients who survived from OHCA for over one year. The Taiwan National Health Insurance (NHI) Database was used in this study. Study and comparison groups were created to analyze the risk of suffering from new-onset postresuscitation comorbidities from 2011 to 2012 (until December 31, 2013). The study group included 1,346 long-term OHCA survivors; the comparison group consisted of 4,038 matched non-OHCA patients. Demographics, patient characteristics, and risk of suffering comorbidities (using Cox proportional hazards models) were analyzed. We found that urinary tract infections ($n = 225$, 16.72%), pneumonia ($n = 206$, 15.30%), septicemia ($n = 184$, 13.67%), heart failure ($n = 111$, 8.25%) gastrointestinal hemorrhage ($n = 108$, 8.02%), epilepsy or recurrent seizures ($n = 98$, 7.28%), and chronic kidney disease ($n = 62$, 4.61%) were the most common comorbidities. Furthermore, OHCA survivors were at much higher risk (than comparison patients) of experiencing epilepsy or recurrent seizures (HR = 20.83; 95% CI: 12.24–35.43), septicemia (HR = 8.98; 95% CI: 6.84–11.79), pneumonia (HR = 5.82; 95% CI: 4.66–7.26), and heart failure (HR = 4.88; 95% CI: 3.65–6.53). Most importantly, most comorbidities occurred within the first half year after OHCA.

1. Introduction

The outcome of patients who suffer from out-of-hospital cardiac arrest (OHCA) is very poor, and postresuscitation comorbidities increase the long-term mortality [1–4]. The incidences of OHCA clearly differ worldwide (5.7, 38, and 32.7 per 100,000 population each month in the United States, Europe, and Korea, resp.) [5]; however, the average rate of survival to discharge is mostly less than 10% (10.6% in the United States, 5% in Japan, and only 0.5% in Malaysia) [6, 7]. Furthermore, some previous studies reported a one-year survival rate of OHCA of only 7.7% to 11.5% on average [8, 9]. Among these discharged patients, up to 16% of them did not survive over one year [4, 10, 11]. One major reason for the large decrease in rate between survival to discharge and one-year survival is the development of postresuscitation comorbidities [4, 12]. Comorbidities can not only be associated with postcardiac arrest syndrome (systemic ischemia/reperfusion injuries, hypoxia, acidosis, and immune/inflammatory over reactions) but can also be related to poor support during the postresuscitation period [8, 9, 13].

Some economic studies have noted that the medical resources consumed for resuscitating OHCA patients and providing long-term care are quite high [14, 15]. One previous study in Taiwan reported that an OHCA survivor would cost approximately USD$ 14,000 on average for in-hospital resuscitation and postresuscitation comorbidities after discharge [16]. In the United Kingdom, the in-hospital cost of each OHCA patient is generally as high as USD$ 61,000 [17]. In fact, for each OHCA survivor, it would cost approximately $USD 6600 to 10,000 per life-year saved for postresuscitation care [18, 19].

Since postresuscitation comorbidities require high medical resources and decrease the chance of long-term survival, knowledge regarding the prevention or early treatment of comorbidities should be emphasized. However, most current studies concerning OHCA have focused on increasing survival rates or neurological outcomes [20, 21]. Information regarding the prevalence of postresuscitation comorbidities, demographics, and patient characteristics is not well known; in particular, data on long-term follow-ups are lacking. In this study, we aim to analyze new-onset postresuscitation comorbidities in patients who survived over one year after OHCA using the Taiwan national health care system database.

2. Methods and Materials

2.1. Data Source. The Taiwan National Health Insurance (NHI) database was used in this study. The NHI has had nearly 100% coverage of the population since its initiation in 1995 [22]. Since 2000, the NHI has collected all declaration data at the end of every year and derived a corresponding database. The NHI database was created to develop public health policy and clinical research. We obtained our data from the Health and Welfare Data Science Center (HWDC) of Taiwan, a database from the Ministry of health and welfare developed by the NHI program, to study postresuscitation comorbidities in OHCA survivors through a secondary analysis (all data were deidentified) of the study period (January 1, 2011, to December 31, 2012). The registered populations in this database were 22,263,417 and 22,362,328 on December 31, 2011, and December 31, 2012, respectively. All OHCA survivors in this period were followed for postresuscitation comorbidities until December 31, 2013 (the same end point).

2.2. Ethical Approval. Data in the NHI database that could be used to identify patients or care providers were scrambled before being sent to the database and were further concealed before being released to the researchers. Therefore, it was impossible to identify individuals from this database by querying the data alone. This study protocol was approved by the Institutional Review Board (IRB) of Changhua Christian Hospital (permission code: 150117).

2.3. Sample Selection and Definition. This is a retrospective cohort study. Two groups (study and comparison groups) were classified in this study. The two groups were both extracted from the database during the study period (January 1, 2011, to December 31, 2012). Each patient had been followed for new-onset comorbidities (or diseases in the comparison group) until the end point (December 31, 2013). The selection methods of the study and comparison groups are summarized in Figure 1.

2.3.1. Definition of Inclusion Criteria of Study Group. Patients in the study group were extracted from the database during the study period using the following two major criteria.

(1) Patients who suffered from their first experience of OHCA and visited the emergency department (ED). The OHCA event was screened by using the International Classification of Diseases, 9th revision, clinical modification codes (ICD-9-CM 798, 798.1, 798.2, 798.9, 799, 799.0, 799.1, and 427.5) in the ED.

(2) Patients who survived over one year after suffering from an OHCA event.

2.3.2. Definition and Inclusion Criteria of the Comparison Group. Comparison patients were randomly selected from the remaining NHI beneficiaries registered in the database. Patients without OHCA were selected as the comparison group after adjusting their age, gender, and follow-up periods to patients in the study group. They three-times outnumbered the study group [23, 24].

2.3.3. Exclusion Criteria. Patients with the following conditions were excluded from this study both in the study and control groups.

(1) Patients who had any history of a cardiac arrest event before the study period.

(2) Patients who had incomplete medical records.

2.3.4. Definition of Postresuscitation Comorbidities. In the study group, postresuscitation comorbidities were defined as a new-onset disease developing one month after survival from OHCA (diseases developed in the first month after OHCA might be directly associated with the original etiology of OHCA; therefore, these diseases were not included). In the comparison group, comorbidities were new-onset diseases developing during the follow-up period.

2.4. Statistical Analysis. The study and comparison groups were selected with SAS (SAS Institute Inc., Cary, NC, USA). The SAS programming language and the results of the analysis were routinely checked by supervisors of the database to ensure that all information was deidentified. Demographics, patient characteristics, and personal histories were reported as the number, percentage, or mean ± standard deviation (SD). Chi-squared test and t-tests were used to analyze the demographics and postresuscitation comorbidities between the study (OHCA survivors) and comparison groups (without OHCA). Furthermore, Chi-squared test was used to analyze the characteristics of the three most common postresuscitation comorbidities in the two groups. Detailed descriptions regarding classifications of the demographic data have been addressed in previous studies (including classifications of patient's economic level, degree of their city urbanization, and location of their residence in terms of geographic regions

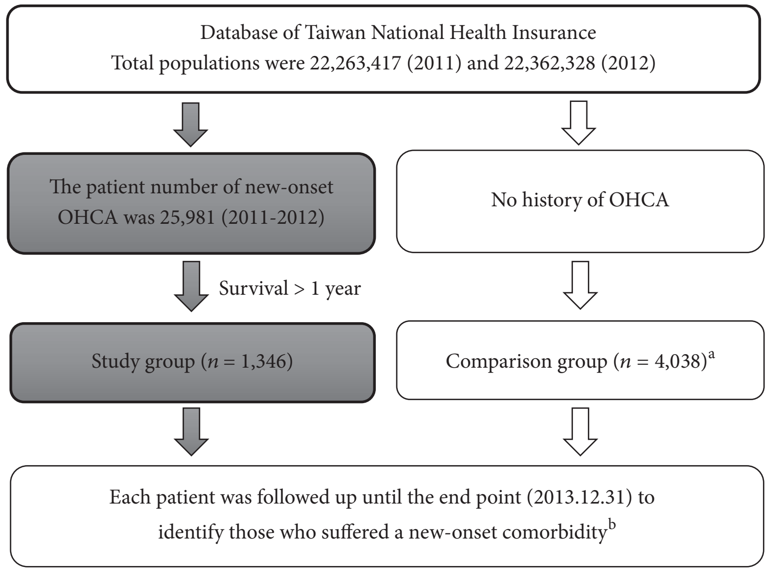


Figure 1: The selection methods of study and comparison patients. [a]Comparison patients were adjusted by age, gender, and follow-up periods to patients in the study group. They three-times outnumbered the study group. [b]New-onset comorbidities in the study group were defined as diseases developed after one month of survival.

in Taiwan) [25, 26]. To analyze the risk of suffering from these comorbidities, crude hazard ratios (HRs) were also calculated (Cox proportional hazards models). Finally, time-related factors associated with the occurrence of postresuscitation comorbidities at different time points in OHCA survivors and comparison patients were also reported. p values < 0.05 were considered statistically significant.

3. Results

3.1. Demographics and Personal Characteristics. The total number of OHCA patients was 13,365 and 12,619 in 2011 and 2012, respectively. The mean incidence of OHCA was 4.8 per 100,000 population (per month). The mean one-year survival rate was only 5.2%. In our study, 1,346 long-term OHCA survivors were enrolled in the study group, whereas 4,038 patients were in the comparison groups. Their characteristics, personal histories, and economic levels are shown in Table 1. Personal history differed significantly between the two groups. OHCA survivors more frequently had histories of cardiac disease, diabetes, hypertension, renal failure, liver cirrhosis, and stroke (all $p < 0.001$). Moreover, OHCA survivors had a clearly lower economic status than comparison patients.

3.2. Postresuscitation Comorbidities. Among the OHCA survivors, the most common postresuscitation comorbidities were urinary tract infections, followed by pneumonia, septicemia, essential hypertension, heart failure, gastrointestinal hemorrhage, epilepsy or recurrent seizures, and chronic kidney disease. Except for essential hypertension ($p = 0.38$), OHCA survivors had significantly higher occurrences than comparison patients of all comorbidities (all $p < 0.001$) (Table 2).

3.3. The Three Most Common Comorbidities between OHCA Survivors and Comparison Patients. The three most common comorbidities were all infection-related diseases (urinary tract infections, pneumonia, and septicemia). Detailed data are shown in Table 3. Of the comparing patients, these three comorbidities were more predominant in the older age group (<75 years) (all $p < 0.001$). However, most OHCA survivors with the three comorbidities were younger than 60 years.

3.4. The Risk of Suffering from Postresuscitation Comorbidities. The HRs of postresuscitation comorbidities during the follow-up period were significantly higher for urinary tract infections (HR = 2.83; 95% CI: 2.37–3.37), pneumonia (HR = 5.82; 95% CI: 4.66–7.26), septicemia (HR = 8.98; 95% CI: 6.84–11.79), gastrointestinal hemorrhage (HR = 3.60; 95% CI: 2.74–4.72), heart failure (HR = 4.88; 95% CI: 3.65–6.53), epilepsy or recurrent seizures (HR = 20.83; 95% CI: 12.24–35.43), and chronic kidney disease (HR = 2.73; 95% CI: 1.95–3.82) (all $p < 0.05$) (Table 4).

3.5. Time of the Occurrence of Postresuscitation Comorbidities. All OHCA survivors were followed to determine the timing of the development of new-onset postresuscitation comorbidities. Most comorbidities occurred in the first half year, including heart failure (56.8%), essential hypertension (59.3%), pneumonia (51.5%), chronic kidney disease (40.3%), epilepsy (56.1%), and urinary tract infections (45.8%). *In this study, we noted that 20.1% of pneumonia events occurred during the 30th day to 60th day after OHCA*. The prevalence of gastrointestinal bleeding was the highest (23.8%) during the period 1 to 1.5 years after OHCA (Figure 2). Finally, among the comparison patients, these diseases did not show a time-related distribution.

Table 1: Characteristics and personal histories of OHCA survivors and comparison patients.

	OHCA survivors (n = 1,346)		Comparison patients (n = 4,038)		
	Number	%	Number	%	p value
Sex					1.000
Male	825	61.29	2475	61.29	
Female	521	38.71	1563	38.71	
Age (mean ± SD, y/o)	55.2 ± 22.9		54.3 ± 22.3		0.199
≦15	106	7.88	318	7.88	1.000
16–30	105	7.80	315	7.80	
31–45	172	12.78	516	12.78	
46–60	335	24.89	1005	24.89	
61–75	336	24.96	1008	24.96	
>75	292	21.69	876	21.69	
Personal history					
Cardiac diseases*	202	15.01	195	4.83	<0.001
Diabetes*	310	23.03	351	8.69	<0.001
Hypertension*	423	31.43	718	17.78	<0.001
Renal failure*	72	5.35	39	0.97	<0.001
Liver cirrhosis*	16	1.19	11	0.27	<0.001
Stroke*	52	3.86	56	1.39	<0.001
Economic level (monthly income in USD$)*					<0.001
<600	415	30.83	1089	26.97	
601–1,000	680	50.52	2014	49.88	
>1,000	250	18.57	926	22.93	
Geographic region of Taiwan*					
Northern	732	54.38	2018	49.98	<0.001
Central	281	20.88	890	22.04	
Southern	272	20.21	1013	25.09	
Eastern	60	4.46	108	2.67	
Urbanization					0.484
1 (most)	328	24.37	1032	25.56	
2	153	11.37	404	10.00	
3	368	27.34	1090	26.99	
4	496	36.85	1503	37.22	

OHCA: out-of-hospital cardiac arrest.
*Significant differences.

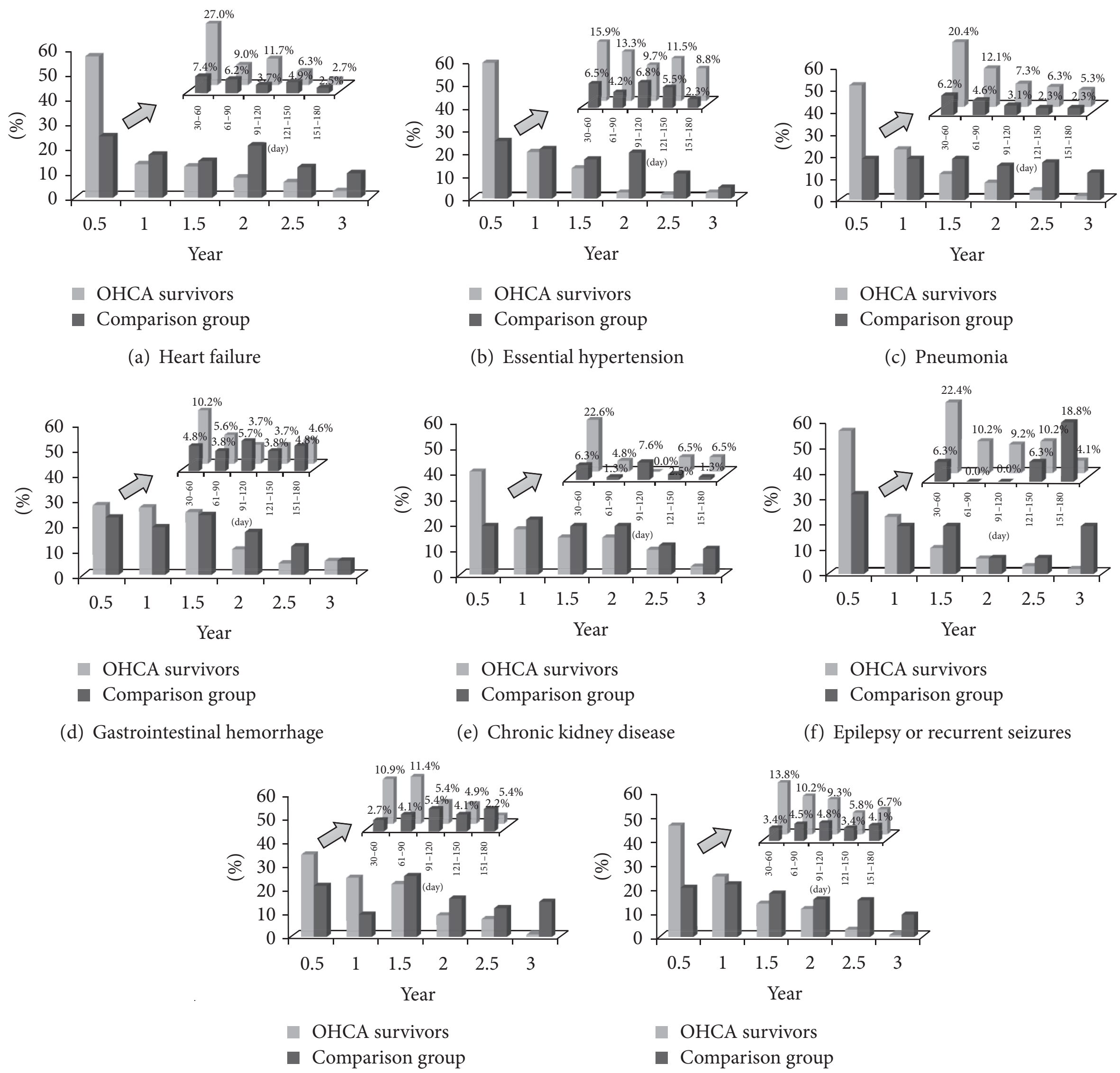
Table 2: Postresuscitation comorbidities of OHCA survivors.

Comorbidities	OHCA survivors		Comparison patients		
	Number	%	Number	%	p value
Urinary tract infections*	225	16.72	290	7.18	<0.001
Pneumonia*	206	15.30	130	3.22	<0.001
Septicemia*	184	13.67	74	1.83	<0.001
Essential hypertension	113	8.40	309	7.65	0.380
Heart failure*	111	8.25	81	2.01	<0.001
Gastrointestinal hemorrhage*	108	8.02	105	2.60	<0.001
Epilepsy or recurrent seizures*	98	7.28	16	0.40	<0.001
Chronic kidney disease*	62	4.61	79	1.96	<0.001

OHCA: out-of-hospital cardiac arrest.
*Significant differences.

Table 3: Significant differences in the three most common postresuscitation comorbidities between OHCA survivors and comparison patients.

	Pneumonia						Septicemia						Urinary tract infections					
	OHCA survivors ($n = 206$)			Comparison patients ($n = 130$)			OHCA survivors ($n = 184$)			Comparison patients ($n = 74$)			OHCA survivors ($n = 225$)			Comparison patients ($n = 290$)		
	Number	%	p value	Number	%	p value	Number	%	p value	Number	%	p value	Number	%	p	Number	%	p value
Sex			0.103			0.361			0.871			0.395			0.940			0.001
Male	137	67		85	65		114	62		47	64		137	61		151	52	
Female	69	33		45	35		70	38		27	36		88	39		139	48	
Age group			0.146			0.000			0.036			0.000			0.088			0.000
≦60	99	48		32	25		83	45		12	16		105	47		108	37	
61–75	62	30		30	23		58	32		22	30		65	29		78	27	
>75	45	22		68	52		43	23		40	54		55	24		104	36	
Economic level (monthly income in USD$)			0.116			0.001			0.162			0.009			0.267			0.006
<600	76	37		44	34		67	36		28	38		78	35		98	34	
601–1,000	97	47		73	56		89	48		39	53		112	50		143	49	
>1,000	33	16		13	10		28	15		7	09		35	16		49	17	
Geographic region of Taiwan			0.305			0.815			0.387			0.085			0.065			0.037
Northern	101	49		64	49		94	51		28	38		111	49		129	44	
Central	50	24		26	20		36	20		17	23		48	21		82	28	
Southern	47	23		37	28		46	25		25	34		59	26		74	26	
Eastern	8	04		3	02		8	04		4	05		7	03		5	02	
Urbanization			0.237			0.047			0.315			0.002			0.501			0.025
1 (most)	60	29		22	17		55	30		12	16		61	27		61	21	
2	26	13		12	09		19	10		9	12		27	12		27	09	
3	54	26		34	26		46	25		11	15		53	24		70	24	
4	66	32		62	48		64	35		42	57		84	37		132	46	



(a) Heart failure

(b) Essential hypertension

(c) Pneumonia

(d) Gastrointestinal hemorrhage

(e) Chronic kidney disease

(f) Epilepsy or recurrent seizures

(g) Septicemia

(h) Urinary treat infections

Figure 2: The prevalence of postresuscitation comorbidities in OHCA survivors. Figures (a) to (h) aim to show when these postresuscitation comorbidities develop during the study period; furthermore, each smaller figure aims to show the detailed prevalence in the first half year.

4. Discussion

Some previous studies have reported that the long-term survival rate of OHCA could be decreased by postresuscitation comorbidities [4, 27, 28]. However, the time points of the occurrence of comorbidities have never been well addressed. In this study, we followed long-term OHCA survivors (survival over one year) and found that most of the comorbidities occurred within the first half year after OHCA.

Among these postresuscitation comorbidities, we noted that cardiovascular diseases and infections were the most prevalent. The risk of suffering new-onset heart failure was clearly higher in OHCA survivors than in comparison patients (HR = 4.88; 95% CI: 3.65–6.53). Moreover, in the first half year, this prevalence among OHCA survivors was 32.1% higher than those in comparison patients. Several possible reasons could contribute to the high prevalence of heart failure. First, the procedure involved in providing chest compression (including manual or device-assisted compression) might not only force circulation but also induce secondary injury of the heart [29]. Some previous studies further demonstrated that myocardial damage, caused by direct physical force, was the second most common CPR-related injury [30–32]. This myocardial damage could influence cardiac contractility, which would increase the chances of heart failure [33–35]. Finally, the elevated levels of inflammatory mediators and nitric oxide production during the postresuscitation period might also cause myocardial injury and further induce heart failure [36, 37]. Therefore, early heart function surveys for preventing or treating heart failure in OHCA survivors might not be avoidable.

Table 4: The risk of suffering from postresuscitation comorbidities in OHCA survivors.

Comorbidities	HR	95% CI	p value
Urinary tract infections*	2.83	2.37–3.37	<0.001
Pneumonia*	5.82	4.66–7.26	<0.001
Septicemia*	8.98	6.84–11.79	<0.001
Essential hypertension	1.23	0.99–1.52	0.059
Heart failure*	4.88	3.65–6.53	<0.001
Gastrointestinal hemorrhage*	3.60	2.74–4.72	<0.001
Epilepsy or recurrent seizures*	20.83	12.24–35.43	<0.001
Chronic kidney disease*	2.73	1.95–3.82	<0.001

HR: hazard ratio; CI: confidence interval.
*Significant differences between OHCA survivors and comparison patients.

Infections were the most common comorbidities in OHCA survivors, in particular pneumonia developed in the early stages after OHCA. The first key factor associated with early pneumonia was brain hypoxic-ischemic injury, which presented early, and reasonably impaired swallowing function and gag reflex (resulting in aspiration pneumonia). In addition, rib fracture was the most common complication of chest compression [30]. These OHCA survivors might suffer from painful breathing and coughing, which would make it difficult to maintain respiratory tract hygiene. As a result, this could increase the chance of suffering from pneumonia [38, 39]. Some previous studies mentioned that early antibiotics for preventing pneumonia in OHCA patients might shorten the duration of hospital stay [40–42]. Unfortunately, prophylactic antibiotics for long-term treatment were not recommended because of a lack of strong evidence. Therefore, the duration of treatment with prophylactic antibiotics might need to be extended to cover this high-risk period (30th to 60th day after OHCA).

In addition to infections, we found that gastrointestinal hemorrhage was also a common postresuscitation comorbidity. Clinically, some treatments for critical cardiovascular events might potentially cause gastrointestinal hemorrhage (i.e., aspirin for acute coronary syndrome could cause peptic ulcer bleeding). Koskinas et al. also reported that gastrointestinal hemorrhage was both a major short-term and long-term complication in patients who received percutaneous coronary interventions [43]. Since peptic ulcers accounted for the majority of gastrointestinal hemorrhage cases, anticoagulation treatments (i.e., aspirin, heparin) for cardiovascular events should be treated more carefully [44]. Although epilepsy or recurrent seizures was not as common as infections or heart failure, the relative risk of these conditions was much higher in OHCA survivors than in comparison patients (HR = 20.83; 95% CI: 12.24–35.43). Almost a third of adult epilepsy cases are caused by brain damage, such as traumatic brain injury and stroke [45–47]. Therefore, we hypothesized that subsequent epilepsy in OHCA survivors could be related to hypoxic-ischemic brain damage during cardiac arrest. Finally, the rule regarding the provision of long-term antiepileptic agents to OHCA survivors was unclear. This study might support the routine treatment of antiepileptic agents in long-term postresuscitation care [48].

5. Limitations

One major limitation of this study is that the different functional levels of survivors were not be distinguished. Most of the comorbidities (including epilepsy, pneumonia, and urinary tract infections) that we identified to be more common in the study group might also be relatively common in patients admitted to rehabilitation facilities or long-term care wards. The conditions of survivors with good neurologic outcomes might differ obviously with those required long-term bed-ridden. Unfortunately, this database we used did not include the detailed neurologic outcome reports. In addition, because the same end point was established, the follow-up period for each OHCA survivor may not have been the same. Detailed quantitative or numeric laboratory reports were not included in this database. Therefore, we could not determine the severity of some complications. For example, this study was not able to identify the stage of chronic kidney disease, classification of heart failure, hemoglobin change in gastrointestinal bleeding, or blood pressure change in infectious disease. The OHCA survivors were not further classified to functional or nonfunctional survivors. The relationship between comorbidities and long-term neurologic outcomes is expected to be further analyzed in the future. Finally, because the facilities for OHCA management and long-term care clearly differ between different countries, the local database in Taiwan used in this study might not truly reflect the conditions in other countries.

6. Conclusions

Long-term OHCA survivors were at a high risk of suffering from heart failure, infections, gastrointestinal hemorrhage, and epilepsy in the postresuscitation period. Most importantly, most of the comorbidities occurred within the first half year after OHCA.

Competing Interests

There is no conflict of interests related to this study.

Authors' Contributions

Chih-Pei Su and Jr-Hau Wu contributed equally to this work.

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Research Article

Saving the On-Scene Time for Out-of-Hospital Cardiac Arrest Patients: The Registered Nurses' Role and Performance in Emergency Medical Service Teams

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For out-of-hospital cardiac arrest (OHCA) patients, every second is vital for their life. Shortening the prehospital time is a challenge to emergency medical service (EMS) experts. This study focuses on the on-scene time evaluation of the registered nurses (RNs) participating in already existing EMS teams, in order to explore their role and performance in different EMS cases. In total, 1247 cases were separated into trauma and nontrauma cases. The nontrauma cases were subcategorized into OHCA (NT-O), critical (NT-C), and noncritical (NT-NC) cases, whereas the trauma cases were subcategorized into collar-and-spinal board fixation (T-CS), fracture fixation (T-F), and general trauma (T-G) cases. The average on-scene time of RN-attended cases showed a decrease of 21.05% in NT-O, 3.28% in NT-C, 0% in NT-NC, 18.44% in T-CS, 13.56% in T-F, and 3.46% in T-G compared to non-RN-attended. In NT-O and T-CS cases, the RNs' attendance can notably save the on-scene time with a statistical significance ($P = .016$ and .017, resp.). Furthermore, the return of spontaneous circulation within two hours ($ROSC_{2h}$) rate in the NT-O cases was increased by 12.86%. Based on the findings, the role of RNs in the EMTs could save the golden time in the prehospital medical care in Taiwan.

1. Introduction

Emergency medical service (EMS) systems may differ depending on the strategies and the plans in the transportation model and the constitution of the EMS team in different countries [1, 2]. More specifically, for the EMS transportation, the Anglo-American model is based on the "patient to doctor" plan, whereas the Franco-German model is based on the "doctor to patient" plan [3–5]. Different transportation models will create different EMS teams, which may consist of emergency medical technicians (EMTs), nurses, and doctors for the prehospital patient care. In Taiwan, the EMS system follows the Anglo-American model, in which patients are transported to hospitals commonly by two EMTs (referred as 2T) [6, 7].

An EMS case can experience various prehospital time intervals [8], such as the response time [9, 10], the on-scene time [11, 12], and a transportation time. Many researchers emphasize shortening the prehospital EMS time in order to save the golden hours for the patient survival [13–20].

Moreover, the on-scene time will be highly affected by the constituent members of an EMS team, compared to the other time intervals, especially in different EMS models [21, 22].

In some countries, the registered nurses (RNs) had become part of the ambulance service [23]; however, the performance of the RNs in the EMS teams could not be evaluated adequately by a standard metric.

Although different EMS teams have been developed in diverse features for different countries, the performance evaluations of RNs in the EMS teams are still challenging the EMS experts, especially in the critical EMS cases such as out-of-hospital cardiac arrest (OHCA) patients [12].

This research focuses on the evaluation of the effects of the on-scene time by introducing one RN into the original EMS team which is formed by two EMTs. Additionally, it investigates the medical benefits of the saved on-scene time; for instance, the methods of the return of spontaneous circulation within two hours ($ROSC_{2h}$) and ED length of stay (LOS) are applied to analyze the clinical impact to the OHCA patients.

2. Materials and Methods

2.1. Study Design. A random participation of the RNs in the EMS teams for prehospital emergency care has been implemented since 2005 at the ChangHua Fire Bureau in Taiwan. In order to evaluate the effects of the RNs in the EMS system, the on-scene time has been analyzed as a primary index to estimate the differentials between these two teams.

The EMS team-attended RNs will receive 46-hour training and participate in programs related to cardiopulmonary resuscitation (CPR), advance cardiac life support (ACLS), and emergency trauma practices. These courses are only offered to nursing personnel with the clinical experience of more than two years.

The RNs accompany two EMTs (referred as 2T1N) in prehospital emergency care from 16:00 to 22:00 in situ every day. When the on-duty RN attends an EMS case, a team of two EMTs (referred as 2T) will be responsible for the subsequent cases until the RN returns to the fire department. On the other hand, once the RN is available, the 2T1N will be teamed again. Accordingly, the participation of the RNs is random, regardless the severity of the EMS cases.

2.2. Setting and Selection of Participants. A total of 1375 EMS cases have been collected from the ChangHua Fire Bureau First Battalion Detachment in Taiwan for the period of August 2010 to January 2011; this is a single center study. The EMT keeps the records of dispatch time, scene arrival time, scene departure time, emergency department (ED) arrival time, and ED departure time [8, 9] as well as the patient information, conditions, scene treatments, and so on. In order to eliminate the outliers of the on-scene time of the two EMS teams, 2T and 2T1N, 128 collected cases (9%) which involve residents with difficult accessibility, drunks, and mentally disordered patients were excluded for the sake of undue bias of the on-scene time. The participation rate of the RNs is 55.81% in this study, while the ED time is defined as the time interval between patient arriving and departing from the EDs.

2.3. Data Collection and Processing. After the case screening, 1247 patients have been separated into the categories of trauma and nontrauma cases. The nontrauma cases are subcategorized into OHCA (NT-O), critical (NT-C) (OHCA excluded), and noncritical (NT-NC) cases, whereas the trauma cases are subcategorized into collar-and-spinal board fixation (T-CS), fracture fixation (T-F), and general trauma (T-G) cases. This assortment is based on the case records of the official EMS sheets provided by EMTs. The patient percentages of the NT-O, NT-C, NT-NC, T-CS, T-F, and T-G cases are 2%, 12%, 21%, 5%, 5%, and 55%, respectively. The on-scene time is defined as the period from the arrival of the ambulance at the scene until the vehicle leaves the scene [11]. During this time period, the EMS teams implement the prehospital first-aid care to the patients. Additionally, the dispatch time is the point where the EMTs are informed for their cases and depart; the scene arrival time is the point where the ambulance reaches the scene and the EMTs get off; the scene departure time is the point where the EMTs complete the patient transfer to the ambulance and the ambulance departs from the scene; the ED arrival time is the point where the ambulance reaches the ED; the ED departure time is point where the EMTs complete the patient handovers [8, 9]. Each time point can be traced and double-checked by the Global Positioning System (GPS) installed in the ambulances. Nevertheless, there are some slight differences of time records between the EMT run reports and the GPS data.

For OHCA cases, the return of spontaneous circulation within two hours ($ROSC_{2h}$) rate refers to the percentage of the OHCA patients who have recovered their pulses after the on-scene triage. All the ED data in this research are obtained from the Changhua Christian Medical Center which is responsible for the critical patients in central Taiwan.

2.4. Primary Data Analysis. All data are extracted from the records on the official EMS sheets, and the on-scene time is obtained from the ambulance scene-departing time minus scene-arriving time. The mathematic method of the arithmetic mean is applied in the average on-scene time calculation, while the statistical significance is determined by the t-test or the F-test with $P < .05$.

The $ROSC_{2h}$ rate of NT-O patients is expressed as the $ROSC_{2h}$ patients divided by the NT-O patients, including the $ROSC_{2h}$ patients therein.

3. Results

The patient flow diagram is shown in Figure 1. A total of 51 patients who live in residences with challenging accessibility are excluded from the 1375 EMS cases, because the on-scene time will be overly extended with significant deviations among the cases. For the same reason, drunks and mentally disordered patients, a total number of 77 are also excluded. After the exclusion of the 128 cases, the remaining 1247 EMS cases receive randomly first aid from 2T or 2T1N teams; more specifically, 551 cases were involved in the 2T teams, while 696 cases were involved in 2T1N teams. Moreover, the cases for both teams were subclassified into six categories of NT-O, NT-C, NT-NC, T-CS, T-F, and T-G, and the patient

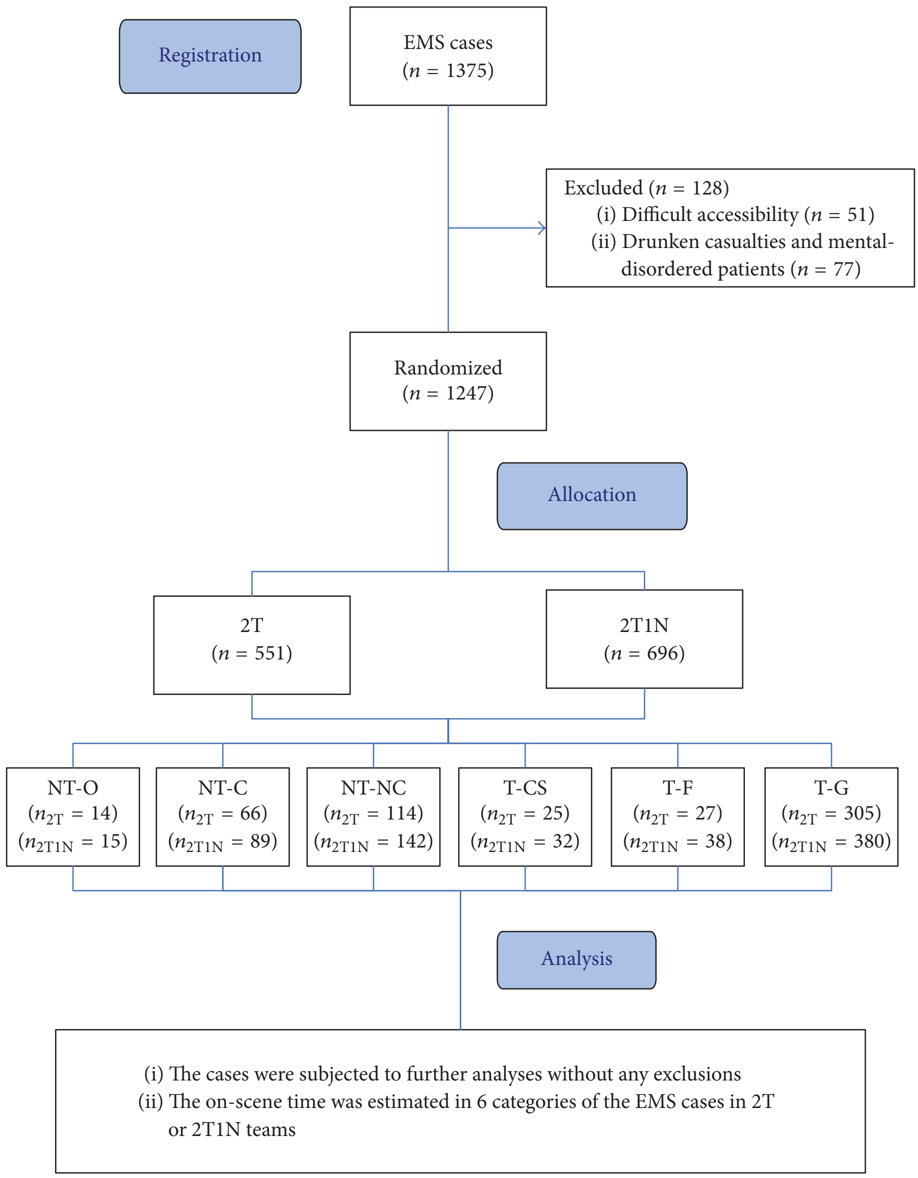

Figure 1: Schematic flow chart of experimental design. 2T, an EMS team with 2 emergency medical technicians; 2T1N, an EMS team with 2 emergency medical technicians and 1 nurse; NT-O, out-of-hospital cardiac arrest (OHCA) patients in nontrauma cases; NT-C, critical patients in nontrauma cases; NT-NC, noncritical patients in nontrauma cases; T-CS, patients with collar-and-spinal board fixation in trauma cases; T-F, patients with fracture fixation in the trauma cases; T-G, general trauma cases.

numbers are indicated as n_{2T} for 2T and as n_{2T1N} for 2T1N teams. Eventually, all the cases of the six categories are subjected to compare the on-scene time between 2T and 2T1N teams.

The average on-scene time of the 2T and 2T1N teams is 6.81 min (with a standard deviation of 2.19 min) and 5.9 min (with a standard deviation of 1.44 min), respectively. For the six types of the EMS cases, the average on-scene time of the NT-O, NT-C, NT-NC, T-CS, T-F, and T-G cases in 2T teams is 8.36 min, 6.41 min, 5.28 min, 9.00 min, 8.04 min, and 4.62 min, whereas in 2T1N teams it is 6.6 min, 6.20 min, 5.28 min, 7.34 min, 6.95 min, and 4.46 min, respectively (Table 1; Figure 2). If the average on-scene time of the 2T teams and the 2T1N teams is compared, a decrease of 1.76 min (21.05%; $P = .016$) in NT-O, 0.21 min (3.28%; $P = .65$) in NT-C, 0 min (0%; $P = .98$) in NT-NC, 1.66 min (18.44%; $P = .017$) in T-CS, 1.09 min (13.56%; $P = .29$) in T-F, and 0.16 min (3.46%; $P = .39$) in T-G cases is noticeable. According to the results of the paired t-test for the average on-scene time of the two teams, only NT-O and T-CS cases have a statistical significance ($P < .05$). Regarding the differences of the average on-scene time between these two teams, the 95% of confidence interval in NT-O cases is between 0.36 and 3.16 min, while in T-CS cases it is between −0.26 and 2.44 min.

As shown in Table 2, the $ROSC_{2\,h}$ rate of the NT-O cases is 7.14% in 2T teams and 20.00% in 2T1N. Furthermore,

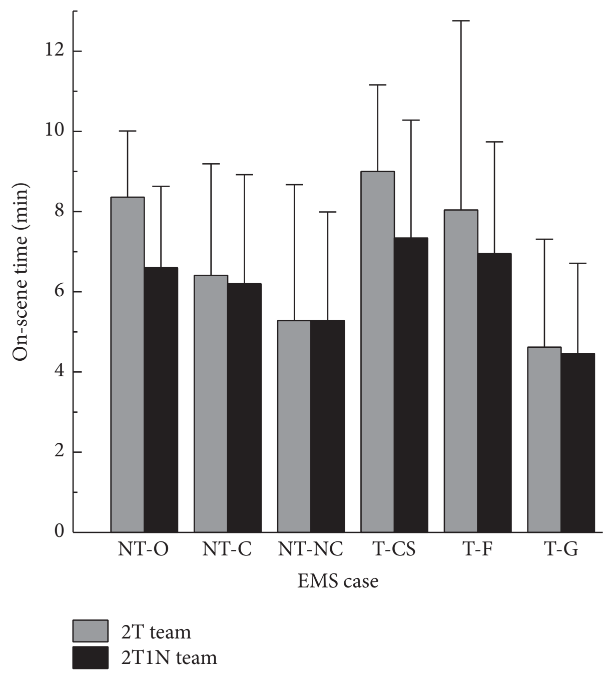

Figure 2: The average on-scene time of the six-categorized EMS cases in 2T and 2T1N teams. 2T, an EMS team with 2 emergency medical technicians; 2T1N, an EMS team with 2 emergency medical technicians and 1 nurse; NT-O, out-of-hospital cardiac arrest (OHCA) patients in nontrauma cases; NT-C, critical patients in nontrauma cases; NT-NC, noncritical patients in nontrauma cases; T-CS, patients with collar-and-spinal board fixation in trauma cases; T-F, patients with fracture fixation in the trauma cases; T-G, general trauma cases.

Table 1: The case numbers and the on-scene time of the six-categorized EMS cases in 2T and 2T1N teams.

EMS case	Case number (person)		On-scene time (min)		P
	2T	2T1N	2T	2T1N	
NT-O	14	15	8.36 ± 1.65	6.60 ± 2.03	.016
NT-C	66	89	6.41 ± 2.78	6.20 ± 2.72	.650
NT-NC	114	142	5.28 ± 3.38	5.28 ± 2.71	.980
T-CS	25	32	9.00 ± 2.16	7.34 ± 2.94	.017
T-F	27	38	8.04 ± 4.72	6.95 ± 2.79	.290
T-G	305	380	4.62 ± 2.69	4.46 ± 2.25	.390

The EMS cases have been collected from the ChangHua Fire Bureau in Taiwan for the period of August 2010 to January 2011.
The on-scene time is presented as mean ± standard deviation in minute (min), and P value is obtained by paired t-test.
2T denotes an EMS team containing 2 emergency medical technicians, while 2T1N denotes 2 emergency medical technicians and 1 nurse in an EMS team.
The nontrauma cases were subcategorized into out-of-hospital cardiac arrest (OHCA) (NT-O), critical (NT-C), and noncritical (NT-NC) cases, while the trauma cases were subcategorized into collar and spinal board fixation (T-CS), fracture fixation (T-F), and general trauma (T-G) cases.

the 2T1N teams have an increase of 12.86% of $ROSC_{2h}$ rate compared to the 2T teams.

Additionally, in order to reveal the interactions between the on-scene time and the ED LOS in 2T and 2T1N teams in six-categorized cases, a statistical method of multivariate analysis of variance (MANOVA) is adopted to perform the F-test.

4. Limitations

The prime limitation of this research is the uncertain cohort of the 2T and the 2T1N teams. Equally important is the unpredictable situations both teams have to encounter in each EMS case. These limitations will cause internal errors while calculating the on-scene time.

Although the benefits of the attendances of the RNs in EMS can be estimated by using the on-scene time, the medical benefits of 2T1N teams to the patients in total could be evaluated by a comprehensive study, and it could focus on the patient aspects of the medical prognosis, the hospital days, and the survival rate.

Based on the EMS recordings, the cases are classified into six types; however some other types may be more important for understanding the real conditions of the participation of the RNs in the EMS teams.

5. Discussion

According to the findings of this research, the 2T1N teams appear to have more medical benefits in saving the on-scene

Table 2: The $ROSC_{2h}$ rate of the NT-O cases in 2T and 2T1N teams.

NT-O case	Case number (person)	
	2T	2T1N
$ROSC_{2h}$	1	3
Total	14	15
$ROSC_{2h}$ rate	7.14%	20.00%

The return of spontaneous circulation within two hours ($ROSC_{2h}$) rate refers to the percentage of the out-of-hospital cardiac arrest (OHCA) patients who have recovered their pulses after reaching the EDs.
2T, an EMS team with 2 EMTs; 2T1N, an EMS team with 2 EMTs and 1 nurse; NT-O, the OHCA patients in nontrauma cases.

time for EMS system compared to the 2T teams. The average on-scene time is 6.81 ± 2.19 min without attendances of RNs, whereas the average on-scene time is 5.9 ± 1.44 min with the attendances. The average on-scene time has a statistic significant decrease of 21.05% in NT-O and 18.44% in T-CS ($P = .016$ and $P = .017$, resp.). The reason for these discrepancies may be that the RNs can govern the cases, especially when ACLS and intravenous infusions for NT-O patients are needed while the EMTs are performing CPR. In addition to that, the RNs in 2T1N teams can give practical medical advices and decision-making during the on-scene emergency care [23]. Furthermore, the RNs can not only provide emergency medical serves of collar or spinal fixation apparatus to T-CS patients but also facilitate the immobilization of the injured portions for such cases. On the other hand, the NT-C, NT-NC, T-F, and T-G cases require less on-scene treatments, so the RNs in a 2T1N team may detract from effectiveness.

For the NT-O cases, the $ROSC_{2h}$ rate is 7.14% in 2T teams, while for the 2T1N it is 20.00%. The participation of the RNs reaches a 12.86% promotion in $ROSC_{2h}$ rate for OHCA patients, which shows that the saved on-scene time and the attendance of RNs could contribute to the real medical benefits of a life-saving purpose [24, 25].

For the sake of the high turnover rate of EMTs in this specific fire department, the study period is limited from August 2010 to January 2011 in order to minimize the effects of the EMT staff discrepancy. During this time period, all the EMTs are the same but may be under different compositions. The nursing staff cannot be controlled in this research, because the cooperative hospital has assigned the RNs programmatically for attending the EMS teams.

Based on the results, all the six-categorized cases show no statistical significance ($P > .05$) between the on-scene time and the ED LOS whether the RNs are attended in the EMS teams or not. The above findings indicate that the ED LOS is an independent event [26] and it is not related to the on-scene time. Therefore, the medical advantages of the attendances of the RNs in the EMS teams should be noticeably evaluated by the methods which exclude the ED time. Nevertheless, the RNs in the EMS teams have a well-communicated practice to report the adequate on-scene physical examinations and triage while transferring the patients to the EDs [23, 27, 28].

Thus far, it remains a challenge to exclude completely the benefits of the RNs attendances in EMS teams from the manpower-added issues. However, the shortage of the on-scene time between the 2T1N and 2T teams is not a solid constant just by reviewing the results of the six-classified cases. The findings of this research may highlight not only the fact that the extra RNs are manpower-added advantages but also medical-based benefits [23, 28]. Based on the EMS practice, the RNs with rich clinical experiences can play a major role in on-scene triage, patient stabilization, leadership assumption, case reporting, decision-making, and first-aid treatment, especially in critical EMS cases [22, 23, 28].

For EMS cases, the on-scene time has a high impact in a compressed window of emergency medical care, while seconds could mean life or death. Therefore, the introduction and participation of RNs in the EMS teams show a plethora of EMS benefits by shortening the on-scene time in the NT-O and T-CS cases and reaching an obvious increase in $ROSC_{2h}$ rate for OHCA patients.

Competing Interests

All authors report no conflict of interests.

Authors' Contributions

Ming-Wei Lin, Chih-Long Pan and Che-Yu Wu conceived the study. This research was first designed by Che-Yu Wu and Ming-Wei Lin. Che-Yu Wu and Ming-Wei Lin collected the data and offered the experience of the real EMS act. Moreover, Jyh-Horng Wen and Zhong Tian altered some ideas and thoughts which were not realistic related to the EMS performance. Zhong Tian and Jyh-Horng Wen did their efforts in mathematical calculations and statistical evaluations. Ming-Wei Lin and Chih-Long Pan performed a literature review and drafted the initial manuscript. Jet-Chau Wen supervised all the details of this work. All authors contributed to revisions of this manuscript. Jet-Chau Wen takes responsibility for the paper as a whole.

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Research Article

Prognostic Analysis for Cardiogenic Shock in Patients with Acute Myocardial Infarction Receiving Percutaneous Coronary Intervention

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Cardiogenic shock (CS) is uncommon in patients suffering from acute myocardial infarction (AMI). Long-term outcome and adverse predictors for outcomes in AMI patients with CS receiving percutaneous coronary interventions (PCI) are unclear. A total of 482 AMI patients who received PCI were collected, including 53 CS and 429 non-CS. Predictors for AMI patients with CS including recurrent MI, cardiovascular (CV) mortality, all-cause mortality, and repeated-PCI were analyzed. The CS group had a lower central systolic pressure and central diastolic pressure (both $P < 0.001$). AMI patients with hypertension history were less prone to develop CS ($P < 0.001$). Calcium channel blockers and statins were less frequently used by the CS group than the non-CS group (both $P < 0.05$) after discharge. Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score, CV mortality, and all-cause mortality were higher in the CS group than the non-CS group (all $P < 0.005$). For patients with CS, stroke history was a predictor of recurrent MI ($P = 0.036$). CS, age, SYNTAX score, and diabetes were predictors of CV mortality (all $P < 0.05$). CS, age, SYNTAX score, and stroke history were predictors for all-cause mortality (all $P < 0.05$). CS, age, and current smoking were predictors for repeated-PCI (all $P < 0.05$).

1. Introduction

Cardiogenic shock (CS) is uncommon in patients with acute myocardial infarction (AMI). However, an AMI complicated by CS is a complex syndrome which may induce low cardiac output and hypotension resulting in multiorgan dysfunction and mortality. Even with the introduction of modern intensive care units (ICUs), advanced medical treatment, and invasive devices, the short-term mortality and morbidity of AMI complicated by CS remain high [1–4]. The mortality rate for AMI complicated by CS after early revascularization, including percutaneous coronary intervention (PCI), is approximately 40% to 60%. In addition, as for age and gender, patients with AMI complicated by CS who are older than 75 years of age may have a higher one-year mortality than their younger counterparts [5, 6]. In addition, compared with men, women suffering from STEMI more often have concurrent CS, according to some studies [7].

In terms of an invasive strategy for CS, there was no difference in 30-day survival rate between PCI and coronary artery bypass graft (CABG) group [8]. On the other hand, the outcome data comparing multivessel with culprit lesion PCI is controversial. Thus, the best revascularization strategy for CS patients remains obscure [9–12].

Long-term prognosis of patients with AMI complicated by CS is still unclear and analysis of predictors for adverse clinical outcomes has not been well studied. Therefore, this study aimed to survey the clinical features and outcomes of patients with AMI complicated by CS compared to those without CS. Moreover, the risk factors for recurrent myocardial infarction (MI), cardiovascular (CV) mortality, all-cause mortality, and repeated-PCI in patients with AMI complicated by CS were analyzed.

2. Methods

2.1. Study Population. A retrospective survey of a prospective database was conducted via medical record review over a period from 2007 through 2014. AMI patients between 20 and 90 years of age were consecutively recruited from the inpatient clinic at Taichung Tzu Chi Hospital, Taiwan. They were divided into two groups: patients with AMI complicated by CS (the CS group) and AMI patients without CS (non-CS group). Patients suffering from out of hospital death (OHCA) and patients with malignancy were excluded from the analysis. All patients were followed up regularly via the outpatient department (OPD). A survey focusing on MI, repeated-PCI, CV mortality, and all-cause mortality was completed for each patient at the end of the study.

2.2. Definition, Data Collection, and Measurement. CS was defined as systemic blood pressure (BP) less than 80/50 mmHg or less than 90/60 mmHg after vasopressor therapy during admission to the emergency department. Diabetes was defined as a fasting plasma glucose level of more than 126 mg/dL, a casual plasma glucose level greater than 200 mg/dL, or a hemoglobin A1c (HbA1c) level of more than 6.5%. Hypercholesterolemia was defined as a serum cholesterol level of more than 200 mg/dL or an LDL-C level of more than 100 mg/dL. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2, which was equal to or more than stage III chronic kidney disease (CKD). Previous MI history was defined as a history of MI prior to admission, accompanied by a threefold elevation of cardiac enzymes from the baseline value.

Measurements of body parameters included body height, body weight, and body mass index (BMI). Baseline biochemical data collected on admission included fasting plasma glucose, serum creatinine, total cholesterol, high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), and serum triglyceride level. As for the hemodynamic data, central aorta systolic pressure and central aorta diastolic pressure during cardiac catheterization were also collected. The central aortic pressure (CAP) was measured via a pigtail catheter while performing a coronary angiography. The angiographic findings included number and distribution of diseased vessels, number of treated vessels, and number of lesions. Left ventricular systolic function was usually calculated via two-dimensional echocardiography. Lesion severity and complexity were evaluated using the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score. Related clinical parameters including baseline characteristics, related risk factors, hemodynamic data, angiographic findings, and treatment strategies such as drug medications after discharge or invasive procedures (balloon angioplasty, bare-metal stent deployment, or drug-eluting stent deployment) were compared between patients with CS and those without CS. In addition, this study attempted to identify the significant predictor of AMI patients developing cardiogenic shock and to analyze the adverse predictors of recurrent MI, CV mortality, all-cause mortality, and repeated-PCI procedures in patients with CS.

Table 1: General characteristics of the study population.

Characteristics	Shock	Without shock	P value
Patient number	$N = 53$	$N = 429$	
Age (years)[a]	62.5 ± 12.1	63.6 ± 13.1	0.573
Height (cm)	1.6 ± 0.1	1.6 ± 0.1	0.685
Weight (kg)	67.3 ± 14.9	66.8 ± 13.2	0.822
BMI (kg/m^2)	25.1 ± 4.5	25.1 ± 3.9	0.986
CSP (mmHg)	110.8 ± 26.7	132.4 ± 23.6	<0.001*
CDP (mmHg)	63.1 ± 17.6	72.2 ± 13.2	<0.001*
Glucose (mg/dL)	169.8 ± 94.6	149.9 ± 76.7	0.084
Cholesterol (mg/dL)	169.9 ± 55.8	179.2 ± 45.1	0.168
HDL (mg/dL)	39.6 ± 19.6	39.5 ± 15.9	0.946
LDL (mg/dL)	103.6 ± 43.4	111.7 ± 38.8	0.158
TG (mg/dL)	133.3 ± 94.1	140.3 ± 83.6	0.569
Serum creatinine (mg/dL)	1.7 ± 1.4	1.8 ± 2.2	0.793

BMI: body mass index; CSP: central aortic systolic pressure; CDP: central aortic diastolic pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TG: triglyceride. *Significant.
[a]Mean standard deviation.

2.3. Statistical Analysis. The patients were divided into two groups: patients with AMI complicated by CS (the CS group) and AMI patients without CS (non-CS group). The independent t-test, chi-squared test, Fisher's exact test, and multivariate logistic regression analysis were used to compare the differences between the two groups. The log rank test and Kaplan-Meier curves were used for the survival analysis. The Cox proportional hazards model was used to test the effects of independent variables on hazards. P values less than 0.05 were considered significant. All analyses were performed using the statistical package SPSS for Windows (Version 23.0, SPSS Inc., Chicago, IL).

3. Results

A total of 482 patients who suffered from AMI were collected during the study period. Among them, there were 53 patients with AMI complicated by CS on admission, while 429 patients had no CS during admission. The mean age in the CS group compared with the non-CS group was 62.5 ± 12.1 years versus 63.6 ± 13.1 years, respectively ($P = 0.573$). The mean follow-up period was 94.4±97.9 weeks for the CS group and 152.2 ± 108.4 weeks for the non-CS group.

Baseline clinical characteristics are shown in Table 1. Concerning the hemodynamic parameters, after inotropic agents and intra-aortic balloon pumping (IABP) usage, the CS group had a lower central systolic pressure (CSP) (110.8 ±

Table 2: Demography of study population and medications during admission in patients with and without shock.

Characteristics	Shock (%)	Without shock (%)	P value
Gender			0.996
Male	41 (77.4)	332 (77.4)	
Female	12 (22.6)	97 (22.6)	
STEMI			0.001*
Yes	36 (67.9)	184 (42.9)	
No	17 (32.1)	245 (57.1)	
Diabetes			0.597
Yes	23 (43.4)	170 (39.6)	
No	30 (56.6)	259 (60.4)	
Hypertension			<0.001*
Yes	13 (24.5)	225 (52.4)	
No	40 (75.5)	204 (47.6)	
CKD			0.662
Yes	28 (52.8)	213 (49.7)	
No	25 (47.2)	216 (50.3)	
Hypercholesterolemia			0.125
Yes	22 (41.5)	226 (52.7)	
No	31 (58.5)	203 (47.3)	
Current smoker			0.981
Yes	23 (43.4)	185 (43.2)	
No	30 (56.6)	243 (56.8)	
Stroke history			0.673
Yes	4 (7.5)	26 (6.1)	
No	49 (92.5)	403 (93.9)	
CABG history			0.369
Yes	1 (1.9)	3 (0.7)	
No	52 (98.1)	426 (99.3)	
Aspirin			0.559
Yes	50 (94.3)	395 (92.1)	
No	3 (5.7)	34 (7.9)	
P2Y12 inhibitors			0.040*
Yes	53 (100)	397 (92.5)	
No	0	32 (7.5)	
Diuretics			0.226
Yes	10 (18.9)	114 (26.6)	
No	43 (81.1)	315 (73.4)	
Beta-blockers			0.549
Yes	24 (45.3)	213 (49.7)	
No	29 (54.7)	216 (50.3)	
CCB			0.012*
Yes	3 (5.7)	85 (19.8)	
No	50 (94.3)	344 (80.2)	
ACEI			0.247
Yes	15 (28.3)	156 (36.4)	
No	38 (71.7)	273 (63.6)	
ARB			0.090
Yes	5 (9.4)	81 (18.9)	
No	48 (90.6)	348 (81.1)	
Statins			0.040*
Yes	14 (26.4)	176 (41.0)	
No	39 (73.6)	253 (59.0)	
Fibrate			0.845
Yes	2 (3.8)	14 (3.3)	
No	51 (96.2)	415 (96.7)	

Previous MI: history of previous myocardial infarction; CABG history: history of coronary artery bypass graft; CKD: chronic kidney disease; P2Y12 inhibitor: P2Y12 receptor inhibitor of platelet; CCB: calcium channel blocker; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker. *Significant.

26.7 versus 132.4 ± 23.6 mmHg, $P < 0.001$) and a lower central diastolic pressure (CDP) (63.1 ± 17.6 versus 72.2 ± 13.2 mmHg, $P < 0.001$) compared with the non-CS group. As for the baseline biochemistry, there was no significant difference between the two groups.

The demographic data of the study population are shown in Table 2. ST-elevation myocardial infarction (STEMI) was more prevalent in the CS group compared with the non-CS group, and non-ST-elevation myocardial infarction was less prevalent in the CS group than in the non-CS group ($P = 0.001$). On the other hand, a history of hypertension was less prevalent in the CS group compared with the non-CS group ($P < 0.001$). In addition, patients in the CS group used P2Y12 receptor inhibitor of platelet (P2Y12 inhibitors) more frequently than those in the non-CS group ($P = 0.04$). By contrast, CCB and statins were less frequently used by the CS group compared with the non-CS group ($P = 0.012$ and $P = 0.04$, resp.).

The angiographic findings and clinical outcomes are shown in Table 3. The distributions of diseased vessels in the CS group compared with the non-CS group were single vessel disease, 34.0% versus 39.2%; dual vessel disease, 30.2% versus 35.2%; and triple vessel disease, 35.8% versus 25.6% ($P = 0.285$). The SYNTAX score was higher in the CS group than in the non-CS group (17.3 ± 10.4 versus 13.1 ± 8.0, $P < 0.001$).

Figure 1 shows the cumulative rate of freedom from recurrent MI, CV mortality, all-cause mortality, and repeated-PCI between the two groups. Freedom from CV mortality, all-cause mortality, and repeated-PCI was lower in the CS group compared with the non-CS group (all $P < 0.001$, resp.), but there was no significant difference between the two groups for recurrent MI ($P = 0.305$).

Medical factors predicting AMI complicated by CS are shown in Table 4. Based on the results of multivariate logistic regression analysis, SYNTAX score was the only predictor of AMI complicated by CS ($P = 0.002$). Furthermore, adverse predictors associated with clinical outcome in patients with AMI complicated by CS are listed in Table 5. For the CS group, history of stroke was a predictor of recurrent MI ($P = 0.036$), and CS, age, SYNTAX score, and diabetes were associated with CV mortality ($P < 0.001$, $P < 0.001$, $P = 0.008$, and $P = 0.047$, resp.). On the other hand, use of beta-blockers (BBs) and angiotensin-converting enzyme inhibitor (ACEIs) could reduce CV mortality. Moreover, CS, age, SYNTAX score, and history of stroke were associated with all-cause mortality ($P < 0.001$, $P < 0.001$, $P = 0.002$, and $P = 0.003$, resp.), whereas use of BBs and statins could

Table 3: Demography of angiographic findings and clinical outcome.

Characteristics	Shock (%)	Without shock (%)	P value
Follow-up time (weeks)[a]	94.4 ± 97.9	152.2 ± 108.4	<0.001
Number of diseased vessel			0.285
Single vessel disease	18 (34.0)	168 (39.2)	
Dual vessel disease	16 (30.2)	151 (35.2)	
Triple vessel disease	19 (35.8)	110 (25.6)	
Mean of treated vessels	1.2 ± 0.5	1.2 ± 0.5	0.612
Mean of treated lesions	1.5 ± 0.7	1.5 ± 0.8	0.805
Lesion location			
LAD	42 (79.2)	335 (78.1)	0.847
LCX	31 (58.5)	237 (55.2)	0.654
RCA	35 (66.0)	232 (54.1)	0.098
SYNTAX score	17.3 ± 10.4	13.1 ± 8.0	<0.001
LVEF	0.5 ± 0.1	0.5 ± 0.1	0.387
Type of intervention			
Balloon angioplasty	12 (22.6)	128 (29.8)	0.276
BMS deployment	28 (52.8)	200 (46.6)	0.393
DES deployment	16 (30.2)	155 (36.1)	0.394
RMI			0.657
Yes	5 (9.4)	33 (7.7)	
No	48 (90.6)	396 (92.3)	
CV death			<0.001
Yes	18 (34.0)	43 (10.0)	
No	35 (66.0)	386 (90.0)	
All-cause death			<0.001
Yes	21 (39.6)	74 (17.2)	
No	32 (60.4)	355 (82.8)	
Re-PCI			0.501
Yes	16 (30.2)	111 (25.9)	
No	37 (69.8)	318 (74.1)	

LAD: left anterior descending artery; Lcx: left circumflex artery; RCA: right coronary artery; SYNTAX score: Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery score; LVEF: left ventricular ejection fraction; BMS: bare-metal stent; DES: drug-eluting stent; RMI: recurrent myocardial infarction; CV death: cardiovascular death; Re-PCI: repeated percutaneous coronary intervention. [a]Median (maximum-minimum).

Table 4: Significant predictors of CS for AMI patients in stepwise multiple logistic regression.

Variable	Adjusted OR	95% CI	P value
Age	0.99	0.96–1.01	0.373
Male	1.10	0.49–2.44	0.825
SYNTAX score	1.05	1.02–1.09	0.002*
Smoke	0.84	0.42–1.67	0.615
Comorbidity			
STEMI	2.05	0.06–70.76	0.691
Non-STEMI	0.69	0.02–23.97	0.838
Dyslipidemia	0.77	0.40–1.51	0.447
Stroke	1.07	0.33–3.42	0.914
Diabetes mellitus	1.04	0.55–1.95	0.906
Medications			
Aspirin	1.48	0.41–5.41	0.549
Diuretics	0.69	0.31–1.54	0.366
BB	0.88	0.47–1.63	0.681
ACEI	0.55	0.27–1.12	0.098
Statin	0.49	0.23–1.02	0.056

Clinical factor used in analysis included sex, baseline biochemical data, angiographic findings on cardiac catheterization, exposed risk factors, and medications during admission. STEMI: ST-segment elevation myocardial infarction; Non-STEMI: non-ST-segment elevation myocardial infarction; BB: beta-blockers; ACEI: angiotensin-converting enzyme inhibitors. *Significant.

reduce all-cause mortality. For repeated-PCI, CS, age, and current smoking were related risk factors ($P < 0.001$, $P = 0.018$, and $P = 0.027$, resp.), whereas usage of ACEIs could reduce the rate of repeated-PCI.

4. Discussion

AMI complicated by CS is one of the leading causes of death in patients hospitalized with AMI. Despite relevant progress even after invasive strategy, prognosis in this population remains poor and risk of future cardiac events is high. In this study, long-term CV mortality, all-cause mortality, and rate of repeated-PCI were higher in the CS group compared with the non-CS group. However, there was no difference between groups regarding recurrent MI. In addition, we found that SYNTAX score was an important risk factor for patients with AMI complicated by CS.

In our study, we also found that both CSP and CDP were lower in the CS group compared with the non-CS group in spite of use of inotropic agents or/and intra-aortic balloon pump (IABP). This finding was compatible with the reduced use of potent hypotensive agents such as CCB and angiotensin receptor blockers (ARB) in the CS group. Moreover, we found that hypertension was more prevalent in the non-CS group compared with the CS group.

The role of hypertension in AMI patients developing CS remains controversial. In a large observational study, the presence of hypertension in AMI patients may protect against developing CS [13], but, according to Menon and colleagues in the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) III Trial, hypertension was a predictor for developing CS in AMI patients [14]. There was no difference in terms of number or distribution of disease vessels from angiographic findings, but the left anterior descending artery (LAD) was the most common location of lesions in patients with AMI complicated by CS.

As has been reported, STEMI occurred more frequently in the CS group, but our CS group had higher SYNTAX scores than our non-CS group, which indicated that they had more complex and more severe lesion anatomy. Simple infarct-related artery (IRA) intervention in the CS group due to STEMI may have led to inadequate revascularization in these cases which could have affected long-term mortality and repeat-PCI rate. Immediate multivessel revascularization may be helpful in patients with CS due to STEMI [9] but

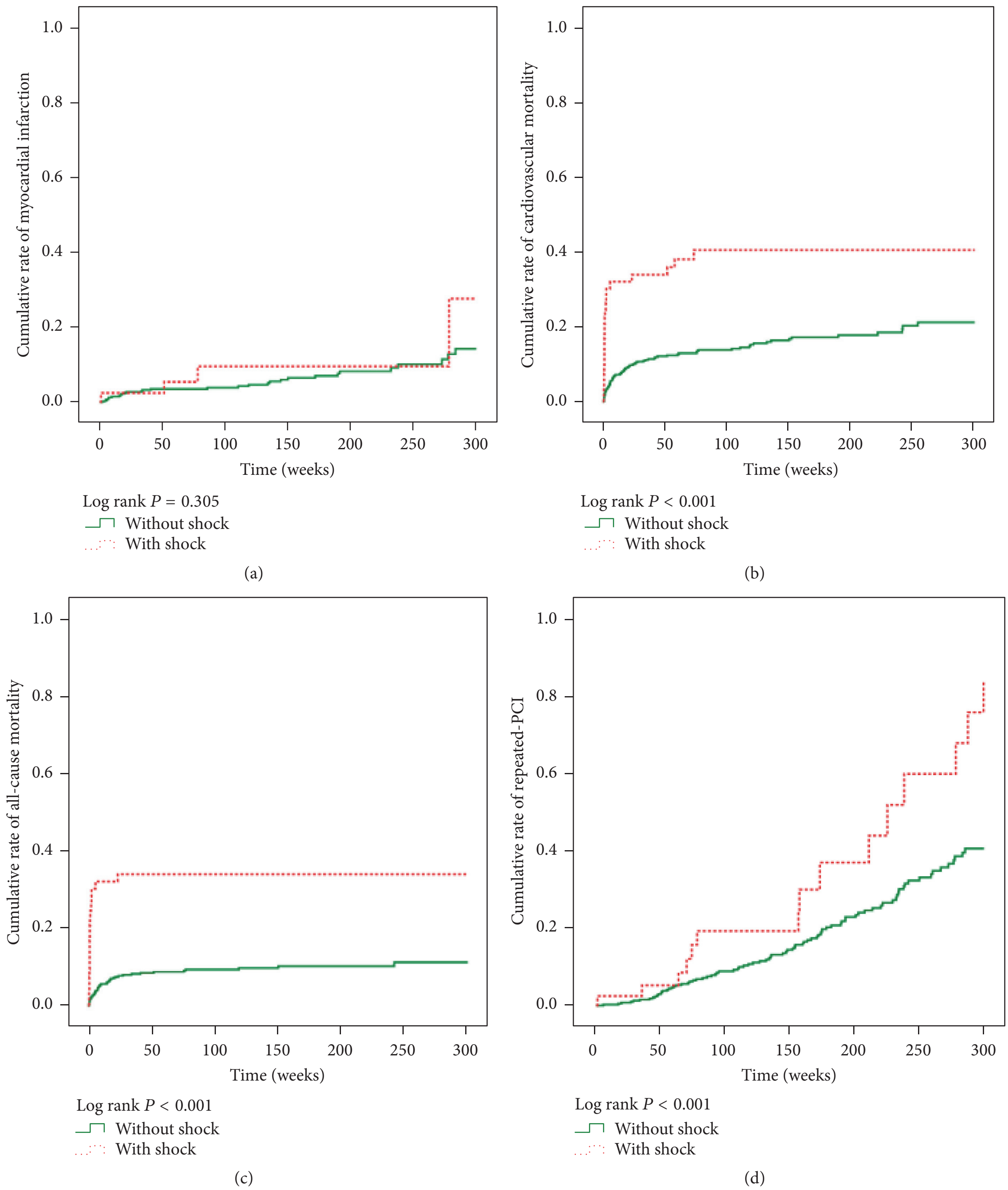

Figure 1: (a) Cumulative rate of myocardial infarction between the two groups ($P = 0.305$). (b) Cumulative rate of cardiovascular mortality between the two groups ($P < 0.001$). (c) Cumulative rate of all-cause mortality between the two groups ($P < 0.001$). (d) Cumulative rate of repeated-PCI between the two groups ($P = 0.001$).

whether this applies to all patients with AMI complicated by CS is still controversial [10].

The 30-day predictors for clinical outcomes of CS such as CS itself, DM, hypertension, previous MI, and old age have been previously studied [15]. From the results of logistic regression analysis, SYNTAX score was the only factor strongly related to developing CS in the AMI patients in our study. On the other hand, based on the results of our Cox proportional hazards model, CS, age, and SYNTAX score were risk factors associated with both long-term CV mortality and all-cause mortality. In patients with acute coronary syndrome (ACS), SYNTAX score was a significant predictor of both short-term and long-term outcomes. For STEMI patients receiving primary PCI, SYNTAX score was an independent

Table 5: Cox proportional hazard ratio of recurrent myocardial infarction, cardiovascular mortality, all-cause mortality, and repeated-PCI in AMI patients with cardiogenic shock after index PCI.

Variable	Recurrent MI		CV mortality		All-cause mortality		Repeat-PCI	
	Adjusted HR	*P* value	Adjusted HR	*P* value	Adjusted HR	*P* value	Adjusted HR	*P* value
With CS	1.57	0.442	4.51	<0.001*	3.66	<0.001*	2.93	<0.001*
Age	1.03	0.094	1.06	<0.001*	1.06	<0.001*	1.02	0.018*
Male	1.42	0.424	0.74	0.332	1.03	0.904	1.08	0.798
SYNTAX score	1.03	0.163	1.03	0.008*	1.03	0.002*	0.98	0.078
Comorbidity								
STEMI	2.53	0.870	2.85	0.308	3.16	0.251	5.02	0.740
Non-STEMI	5.78	0.758	3.28	0.258	4.72	0.128	6.20	0.707
DM	1.89	0.087	1.76	0.047*	1.46	0.088	1.54	0.043
Dyslipidemia	0.91	0.817	0.91	0.737	0.98	0.931	0.87	0.540
Smoke	0.63	0.273	1.13	0.724	0.80	0.403	1.67	0.027*
Stroke	3.19	0.036*	2.04	0.075	2.53	0.003*	1.09	0.873
Medications								
Aspirin	0.86	0.814	1.42	0.463	0.60	0.068	1.98	0.191
P2Y12 inhibitors	0.84	0.778	2.03	0.336	0.90	0.790	1.51	0.384
Diuretics	1.33	0.466	1.09	0.793	1.02	0.937	1.27	0.355
BB	0.83	0.610	0.42	0.005*	0.50	0.004*	1.02	0.938
ACEI	1.06	0.889	0.48	0.032*	0.64	0.078	0.41	<0.001*
Statin	0.67	0.379	0.57	0.129	0.50	0.023*	0.93	0.784

Recurrent MI: recurrent myocardial infarction; CV mortality: cardiovascular mortality; CS: cardiogenic shock; SYNTAX score: Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery score; DM: diabetes mellitus; STEMI: ST-segment elevation myocardial infarction; Non-STEMI: non-ST-segment elevation myocardial infarction; P2Y12 inhibitors: P2Y12 receptor inhibitor of platelet; BB: beta-blockers; ACEI: angiotensin-converting enzyme inhibitors *Significant.

predictor of short-term [16, 17] and long-term cardiac mortality [18, 19]. For NSTEMI patients receiving primary PCI, SYNTAX score was also an independent predictor of 1-year major adverse cardiac events (MACE) including death, cardiac death, MI, and target vessel revascularization (TVR) [20]. Clinically, SYNTAX score should be carefully evaluated during the index catheterization. AMI patients with high SYNTAX score deserve more attention, and more aggressive revascularization should be considered in these patients.

5. Conclusion

Patients with AMI complicated by CS may have higher long-term mortality rates and higher repeated-PCI rates than those without CS, but we found no significant difference in the occurrence of recurrent MI between the two groups. SYNTAX Score strongly correlated with development of CS in AMI patients during initial admission and may also predict long-term mortality in AMI patients with CS.

Abbreviations

ACEI: Angiotensin-converting enzyme inhibitor
AMI: Acute myocardial infarction
ARB: Angiotensin receptor blocker
BB: Beta-blockers
BMI: Body mass index
BMS: Bare-metal stent
CAD: Coronary artery disease
CABG: Coronary artery bypass graft
CCB: Calcium channel blockers
CKD: Chronic kidney disease
CDP: Central aortic diastolic pressure
CSP: Central aortic systolic pressure
CS: Cardiogenic shock
CV mortality: Cardiovascular mortality
DES: Drug-eluting stent
eGFR: Estimated glomerular filtration rate
FFR: Fraction flow reserve
HbA1c: Hemoglobin A1C
HDL-C: High-density lipoprotein-cholesterol
LAD: Left anterior descending artery
Lcx: Left circumflex artery
LDL-C: Low-density lipoprotein-cholesterol
LVEF: Left ventricular ejection fraction
OPD: Outpatient department
PCI: Percutaneous coronary intervention
RCA: Right coronary artery
SYNTAX score: Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery score
TG: Triglyceride.

Additional Points

Study Limitations. Our study had some limitations including geographical and country differences in invasive strategy which may have caused treatment bias and subsequent impact on outcomes. In addition, myocardial perfusion assessment such as Thrombolysis in Myocardial Infarction (TIMI) flow was not evaluated in this study. Thrombus aspiration and IABP insertion were also not routinely performed in this study, which may have had an impact on outcomes.

Ethical Approval

The study protocol was approved by the Institution Review Board and ethics committee of Taichung Tzu Chi Hospital (REC105-26).

Consent

The requirement of individual patient consent was unnecessary because of the retrospective design.

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

Mao-Jen Lin and Han-Ping Wu conceived and designed the study. Chun-Yu Chen participated in data analysis. Hau-De Lin gathered the data. Mao-Jen Lin and Han-Ping Wu drafted the manuscript, with all authors revising it critically for intellectual content. All authors have read, reviewed, and approved the final version of this manuscript for publication.

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Research Article

Early Administration of Glutamine Protects Cardiomyocytes from Post-Cardiac Arrest Acidosis

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Postcardiac arrest acidosis can decrease survival. Effective medications without adverse side effects are still not well characterized. We aimed to analyze whether early administration of glutamine could improve survival and protect cardiomyocytes from postcardiac arrest acidosis using animal and cell models. Forty Wistar rats with postcardiac arrest acidosis (blood pH < 7.2) were included. They were divided into study (500 mg/kg L-alanyl-L-glutamine, $n = 20$) and control (normal saline, $n = 20$) groups. Each of the rats received resuscitation. The outcomes were compared between the two groups. In addition, cardiomyocytes derived from human induced pluripotent stem cells were exposed to HBSS with different pH levels (7.3 or 6.5) or to culture medium (control). Apoptosis-related markers and beating function were analyzed. We found that the duration of survival was significantly longer in the study group ($p < 0.05$). In addition, in pH 6.5 or pH 7.3 HBSS buffer, the expression levels of cell stress (p53) and apoptosis (caspase-3, Bcl-xL) markers were significantly lower in cardiomyocytes treated with 50 mM L-glutamine than those without L-glutamine (RT-PCR). L-glutamine also increased the beating function of cardiomyocytes, especially at the lower pH level (6.5). More importantly, glutamine decreased cardiomyocyte apoptosis and increased these cells' beating function at a low pH level.

1. Introduction

The survival rate for out-of-hospital cardiac arrest (OHCA) is very low [1–4]. Most sustained return of spontaneous circulation (ROSC) OHCA patients still die from post-cardiac arrest injuries [5–8]. These post-cardiac arrest injuries are critical and systemic reactions, including inflammatory overreactions, failed immune regulation, free-radical attack, and acidosis [2, 9, 10]. Among these injuries, acidosis might start before the event that triggers cardiac arrest (such as a respiratory problem causing respiratory acidosis or infection causing metabolic acidosis), and the severity of the acidosis could become more severe once the circulation collapses (tissue ischemia/reperfusion injury, hypoxia, and free radicals all contribute to acidosis) [6, 9, 11, 12].

The cells of vital organs have been demonstrated to be at risk of apoptosis at low pH levels [13–15]. Furthermore, certain previous studies have reported that early, effective treatment for acidosis might decrease vital organ damage and further increase the survival rate [16, 17]. Therefore, sodium bicarbonate was initially recommended to treat post-cardiac arrest acidosis to restore the acid-base balance, and over the past 30 years, it was even suggested in standard resuscitation guidelines [18, 19]. Unfortunately, recent studies noted major side effects for sodium bicarbonate used for post-cardiac arrest acidosis (including inactivation of simultaneously administered catecholamines, reduction of systemic vascular resistance, hyperosmolality, extracellular alkalosis despite intracellular PCO_2 excess*w* and hypernatremia), and it is no longer recommended in new resuscitation guidelines [18, 20, 21]. Therefore, effective and safe medication for treating post-cardiac arrest acidosis is still lacking.

Glutamine, traditionally considered to be a nonessential amino acid, is now considered as conditionally essential following critical illness and sepsis [22–24]. Recently, glutamine was demonstrated to increase ammoniagenesis and gluconeogenesis in the kidney. Excretion of the resulting ammonium ions increased the excretion of acid, whereas the combined pathways also contributed to the production of HCO_3 (−) ions [25–29]. Therefore, we suspected that glutamine might be a potential medication for treating post-cardiac arrest acidosis. In the present study, we aimed to analyze whether early administration of glutamine could improve survival and protect cardiomyocytes from post-cardiac arrest acidosis using animal and cells models.

2. Materials and Methods

2.1. Ethics Statement. A total of 43 10-week-old male Wistar rats (301–325 g in weight) obtained from BioLASCO Taiwan Co. Ltd. (Taipei, Taiwan) were used to analyze the *in vivo* treatment effect of glutamine in this study. Before the start of the study, all animals were fasted for 12 hours but given free access to water. The protocol was approved by the Committee on the Ethics of Animal Experiments of Changhua Christian Hospital (Permit Number: CCH-AE-104-005) and adhered to the recommendations of the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health.

2.2. Setup of Animal Cardiac Arrest Model: Airways, Intravenous Line, and Measurements of Vital Signs. All rats were anesthetized with isoflurane via inhalation. After short-term inhalation, endotracheal tube (16-gauge polyethylene catheter mounted on a blunt-tipped needle) intubation was performed using the BioLITE Intubation Illumination System®. The rats were ventilated with controlled intermittent positive pressure ventilation (IPPV) (Hallowell EMC Model AWS™) with a tidal volume of 7 mL/kg, a respiratory rate of 80/min, and a fractional inspired oxygen reading of 1.0. A 24-gauge polyethylene catheter (Becton-Dickinson) was advanced into the tail vein for drug administration. Moreover, the cardiac rhythms were measured via Leads I and II using subcutaneous needles (Bio Amp cable and leads, LabTutor® PowerLab, ADInstruments). Blood pressure was measured in the tails of the rats (BP-2000 SERIES II®, noninvasive blood pressure analysis system). The rectal temperature was maintained at 37.0 ± 0.5°C during the experimental period.

2.3. Six Minutes of Global Ischemia to Induce Post-Cardiac Arrest Acidosis (pH < 7.2). Cardiac arrest was induced in all 43 rats by stopping the IPPV and clamping the endotracheal tube to induce asphyxia. Cardiac arrest was confirmed based on an abrupt decrease in systolic arterial pressure to less than 30 mmHg or cardiac rhythms that revealed asystole, ventricular tachycardia/ventricular fibrillation (VT/VF), or pulseless electrical activity (PEA). Immediately after 6 minutes of global ischemia, resuscitation started (blood was also withdrawn for analyzing the pH level). To prevent delay of resuscitation by waiting for pH data, each rat immediately underwent the resuscitation procedures, including (1) mechanical ventilation (100% O_2, respiratory rate of 60 breaths/min), (2) chest cardiac massage (200 times/min, as performed by a mechanical device), and (3) intravenous epinephrine (0.02 mg/kg). However, if a rat did not reach post-cardiac arrest acidosis (pH < 7.2), it was not included in this study ($n = 3$). Once the rats had their spontaneous circulation restored, the cardiac massage and epinephrine administration were no longer provided. Ultimately, a total of 40 rats that were confirmed to have post-cardiac arrest acidosis and that received resuscitation were included in this study.

2.4. Treatment of Rats with Post-Cardiac Arrest Acidosis. All 40 rats were randomly divided into two groups (each $n = 20$), receiving a single administration of 500 mg/kg L-alanyl-L-glutamine (Dipeptiven®, study group) or normal saline (control group) intravenously before resuscitation was started. All rats were treated with the same volume (1 mL) via intravenous injection.

2.5. Assessment of Secondary Outcomes: Sustained ROSC. In this study, sustained ROSC was defined by spontaneous cardiac rhythm in conjunction with a rise in mean arterial pressure to greater than 50 mmHg for at least 20 minutes [30]. After 30 minutes of unsuccessful cardiopulmonary resuscitation (CPR), resuscitation was stopped, and the animals were declared dead. The rates of sustained ROSC in the study and control groups were recorded.

2.6. Assessment of Primary Outcomes: Duration of Survival. For each rat that achieved successful resuscitation, hemodynamic measurements (blood pressure, cardiac rhythms) and ventilation were performed for 72 hours maximum. The duration of survival for each rat in the study and control groups was recorded (the maximal observation time was also 72 hours).

2.7. Normal Human Cardiomyocyte Preparation (iPSC-Derived Cardiomyocytes). In this study, induced pluripotent stem cells (iPSCs) were obtained from the Bioresource Collection and Research Center, Food Industry Research and Development Institute (Taiwan), and cultured on Matrigel-coated plates (mTESR medium). The detailed protocols for the iPSC culture and harvesting of iPSC-derived cardiomyocytes adhered to the protocols in previously published studies [31, 32].

2.8. Quantitative (Flow Cytometry) and Qualitative (Immunostaining) Analyses. The iPSC-derived cardiomyocytes were checked for transdifferentiation efficiency and cell protein/morphology by quantitative (flow cytometry) and qualitative (immunostaining) analyses, respectively [31]. The cells were detached with Accutase solution (Nalgene) and harvested for quantitative analysis by flow cytometry (BD FACSCanto™ II System). The fixation/permeabilization procedure was performed using the BD Cytofix/Cytoperm kit (BD Pharmingen™). The percentage of cardiomyocytes was calculated by staining with phycoerythrin- (PE-) conjugated anti-human cTnT antibody (BD Pharmingen™). All the samples were stained with the corresponding isotype control (BD Pharmingen™) to ensure specificity. Finally, the data were analyzed with flow cytometry software, and the transdifferentiation efficiency was calculated. In addition, cardiomyocytes were fixed in 4% paraformaldehyde and incubated with antibodies for immunostaining [31, 33]. Antibodies against heart-associated proteins, including anti-human cTnT and NKX2.5 (Human Cardiomyocyte Immunocytochemistry Kit, Life Technologies, Invitrogen), were also used for staining to confirm the morphology of the cardiomyocytes. Finally, the nuclei were stained with DAPI. The immunofluorescence images were visualized with a microscope system, and the cell morphology was recorded at different magnifications.

2.9. Exposure to Different pH Levels and RT-PCR Analysis of mRNA Expression of Cell Stress/Apoptosis Markers. The cultured cardiomyocytes were dissociated and equally divided into 5 groups to test the treatment effect of L-glutamine at different pH levels: group A (normal culture medium), group B (pH 6.5 HBSS buffer), group C (pH 6.5 HBSS buffer plus 50 mM L-glutamine), groups D (pH 7.3 HBSS buffer), and group E (pH 7.3 HBSS buffer plus 50 mM L-glutamine). The exposure time in each group was the same (2 hours). Finally, the cardiomyocytes in each group were harvested to analyze the mRNA expression of cell stress and apoptosis markers (caspase-3, Bcl-xL, and p53) using RT-PCR (30 cycles).

2.10. Different pH Exposure and Beating Function of Cardiomyocytes. The iPSC-derived cardiomyocytes that we used in this study exhibited regular beating, and the beats per minute (BPM) of the cells could be directly observed. To analyze the treatment effect of L-glutamine on the beating function, cardiomyocytes were equally divided into 5 groups (groups A to E; the conditions of each group are mentioned above). The exposure time in each group was also 2 hours. During treatment, the BPM in each group were recorded (0, 15, 30, 45, 60, and 120 minutes after treatment with L-glutamine). All experiments were independently performed three times.

2.11. Data Analysis. A chi-squared test, Fisher's exact test, and one-way ANOVA were used in this study. For the animal study, the descriptive analyses of the independent variables (clinical features) assessed in the study and control rats are reported as percentages and the mean ± standard deviation (SD). The relationships between L-alanyl-L-glutamine and the duration of survival in rats with post-cardiac arrest acidosis were analyzed using survival analyses (Kaplan-Meier curves). Finally, the mean BPM of the cardiomyocytes in each group (groups A to E) were compared using one-way ANOVA at different time points after treatment with L-glutamine. A p value < 0.05 was considered statistically significant. All of the analyses were performed using the SPSS statistical package for Windows (Version 15.0, SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Primary Outcomes of Rats with Post-Cardiac Arrest Acidosis. The primary and secondary outcomes are shown in Figure 1. The rates of sustained ROSC were 65% ($n = 13$) and 55% ($n = 11$) in the study and control groups, respectively. In all, only 7 rats survived over 24 hours. The clinical features of the rats with post-cardiac arrest acidosis are shown in Table 1. Between the study and control groups (each $n = 20$), the severities of post-cardiac arrest acidosis were nearly equal. The duration of asphyxia (used for inducing cardiac arrest) and the CPR duration were both not significantly different between the two groups. Although the percentages of achievement of sustained ROSC and survival over 24 hours were both higher in the study group than in the control group, the results were statistically significant.

3.2. Outcomes of Survival Analysis. The duration of survival was significantly longer in the study group than in the control group ($p < 0.05$) (Figure 2).

3.3. Efficiency of Cardiomyocyte Transdifferentiation from iPSCs. The flow cytometry analysis showed that the efficiency of cardiomyocyte transdifferentiation from iPSCs was 85.2% (Figure 3(a)). In this study, these cardiomyocytes presented with functional and regular beating. Immunostaining of these cells revealed that they were positive for cTnT and NKX2.5, which confirmed that the cells that we derived from iPSCs and used in this study were cardiomyocytes (Figures 3(b), 3(c), and 3(d)).

3.4. L-Glutamine Might Protect Cardiomyocytes from Apoptosis Caused by Acidosis. In pH 6.5 or pH 7.3 HBSS buffer, the cell stress (p53) and apoptosis (caspase-3, Bcl-xL) markers exhibited obviously lower expression in cells treated with 50 mM L-glutamine than in those without treatment with L-glutamine (based on 30 cycles of RT-PCR) (Figure 3(e)). These findings suggest that L-glutamine might protect cardiomyocytes from apoptosis caused by acidosis.

3.5. L-Glutamine Increases the Beating Function of Cardiomyocytes, Especially under Lower pH Conditions. The cardiomyocytes (derived from iPSCs and with beating function) were treated with normal culture medium or pH 7.3 or 6.5 HBSS buffer (with or without 50 mM L-glutamine) for 120 minutes. During this period, the mean BPM values were 23.1 ± 0.8 (culture medium), 15.7 ± 0.9 (pH 7.3 HBSS buffer), 34.4 ± 1.0 (pH 7.3 HBSS buffer with 50 mM glutamine), 12.8 ± 0.6

Table 1: Clinical features of rats with post-cardiac arrest acidosis.

	Total of 40 rats with post-cardiac arrest acidosis		
	Study group ($n = 20$) Number (%)	Control group ($n = 20$) Number (%)	p value
Initial blood pH level (mean ± SD)	7.056 ± 0.091	7.058 ± 0.088	0.958
Duration of asphyxia* (mean ± SD) (min)	13.1 ± 3.8	12.4 ± 3.9	0.537
Duration of CPR (mean ± SD) (min)	11.7 ± 4.6	11.5 ± 4.5	0.938
Sustained ROSC	13(65)	11(55)	0.374
Survival over 24 hours	4(20)	3(15)	0.500

*Asphyxia performed to induce cardiac arrest. CPR: cardiopulmonary resuscitation. ROSC: return of spontaneous circulation.

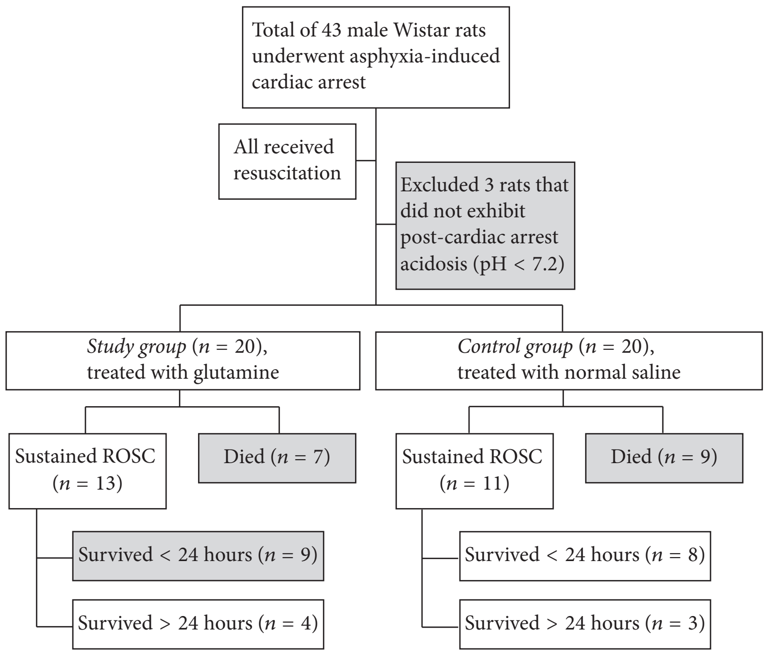


Figure 1: Primary outcomes of rats with post-cardiac arrest acidosis.

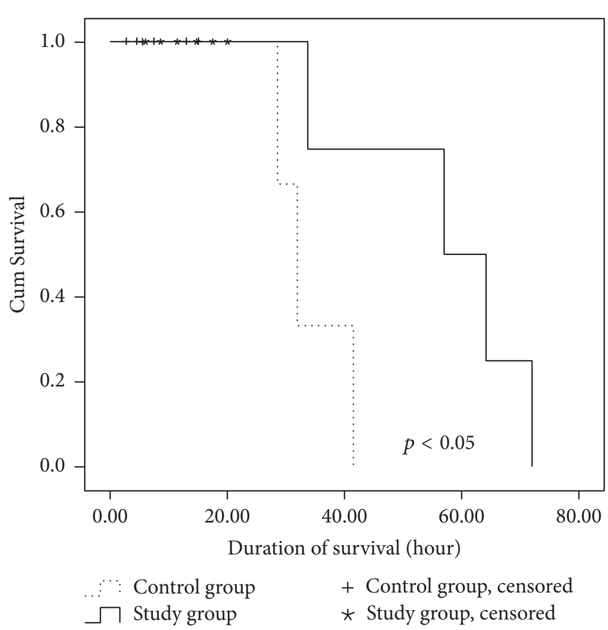


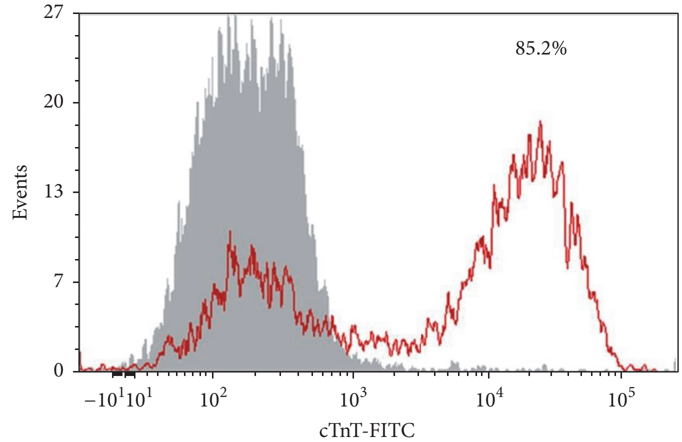
Figure 2: The duration of survival was significantly longer in the study group than in the control group ($p < 0.05$).

(pH 6.3 HBSS buffer), and 55.4 ± 0.9 (pH 6.3 HBSS buffer with 50 mM glutamine) (Figure 4). Generally, the mean BPM was significantly higher among cells treated with 50 mM L-glutamine in pH 7.3 or pH 6.5 HBSS buffer than among those that were not treated with L-glutamine. The cardiomyocytes were nearly not beating from the 45th minute after pH 6.5 exposure, but additional exposure to 50 mM L-glutamine could maintain and even increase the mean BPM of the cells.

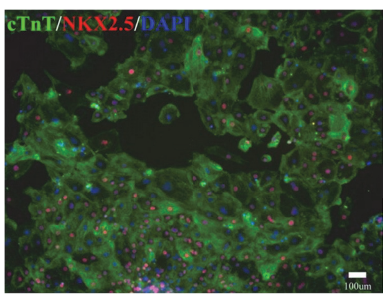
4. Discussion

The primary outcomes of this animal study of cardiac arrest demonstrated that rats treated with early glutamine survived longer than those without glutamine (a positive finding of the survival analysis). Four major explanations might account for this finding.

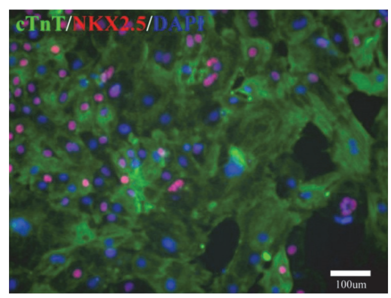
Firstly, glutamine might effectively control systemic post-cardiac arrest injuries. Severe inflammatory reactions (complement activation and IL-1, IL-6, IL-8, and IL-10 elevation), blood coagulation, platelet activation with formation of thromboxane A2, alteration of soluble E-selectin (sE-selectin) and P-selectin (sP-selectin), and whole-body ischemia/reperfusion injury, which occur in sepsis, also occur



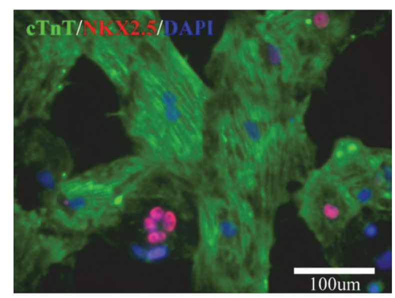
(a)



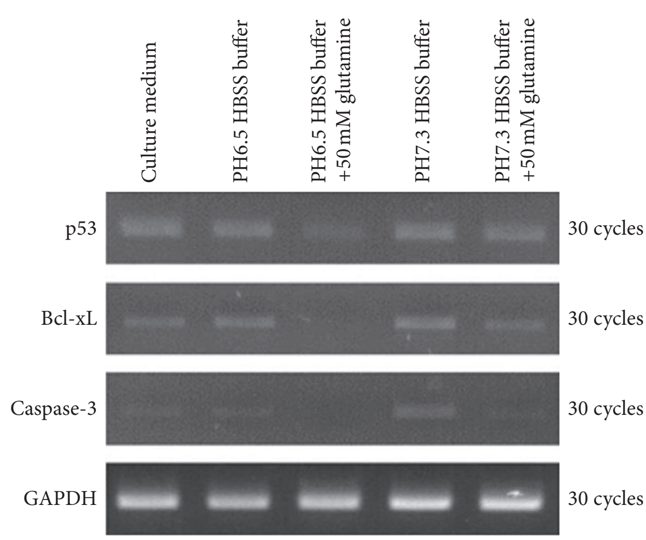
(b)



(c)



(d)



(e)

Figure 3: Assessments of both the efficiency of cardiomyocyte transdifferentiation from iPSCs and the outcomes of low pH exposure. (a) Flow cytometry analysis showing that the differentiation efficiency of cTnT+ cells was 85.2%. (b–d) Cardiomyocytes with positive immunostaining for cTnT, NKX2.5, and DAPI at different magnifications. Scale bars: 100 um. (e) RT-PCR results showing that cardiomyocytes treated with 50 mM L-glutamine exhibited decreased expression of caspase-3, Bcl-xL, and p53 in both pH 6.5 and pH 7.3 HBSS buffers. These findings suggest that L-glutamine might protect cardiomyocytes from apoptosis caused by acidosis. Cell groups: A (normal culture medium), B (pH 6.5 HBSS buffer), C (pH 6.5 HBSS buffer plus 50 mM L-glutamine), D (pH 7.3 HBSS buffer), and E (pH 7.3 HBSS buffer plus 50 mM L-glutamine).

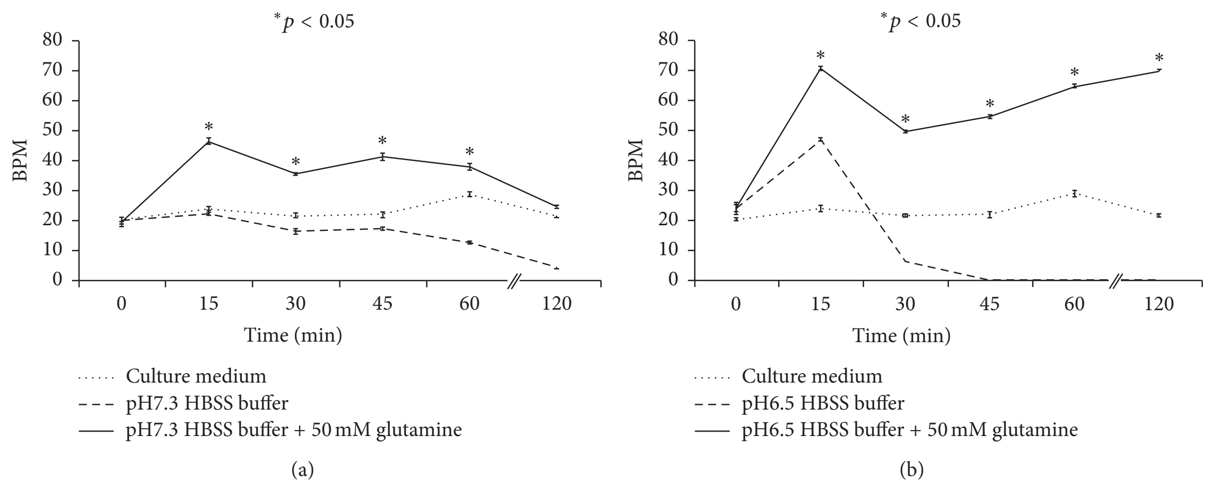


Figure 4: L-glutamine increased the beating function of cardiomyocytes, especially under lower pH conditions. (a) The mean BPM of cardiomyocytes was significantly higher among cells treated with 50 mM L-glutamine in pH 7.3 HBSS buffer than among those that were not treated with L-glutamine. (b) Cardiomyocytes were nearly not beating from the 45th minute after pH 6.5 exposure, but additional exposure to 50 mM L-glutamine could maintain and increase the mean BPM of the cells. One-way ANOVA was used at different time points after treatment with L-glutamine. BPM: beats per minute.

in post-cardiac arrest injuries [6, 9, 34, 35]. Since glutamine is well known as a treatment for sepsis (i.e., due to tissue protection, anti-inflammatory/immune reactions, preservation of tissue metabolic functions, and antioxidant activity/attenuation of inducible nitric oxide synthase expression) [36–39], we believed that early glutamine administration would also be beneficial to patients in the postresuscitation period.

Secondly, we suspect that glutamine can indirectly improve acidosis by increasing ammoniagenesis in the kidney. Several previous studies focused on the acid-base balance reported that the renal proximal tubule could obviously increase the uptake and catabolism of glutamine during acidosis [26–29]. Moreover, the increased catabolism of glutamine triggers ammoniagenesis. Excretion of the resulting ammonium ions facilitates the excretion of acid, whereas the combined pathways accomplish the production of HCO_3 (−) ions, which enter the plasma to restore the acid-base balance [29, 40]. One study further noted that expression of the glutamine transporter Slc38a3 increased in the kidney during metabolic acidosis [25]. Therefore, we suspect that the acid-base balance could be best restored by glutamine supplementation in the early postresuscitation period.

Thirdly, glutamine might directly decrease the apoptosis of cardiomyocytes at a low pH level. In our in vitro study, the expression of caspase-3 and Bcl-xL in cardiomyocytes was obviously decreased following early treatment with glutamine. Clinically, cardiovascular events (i.e., arrhythmia, contraction force dysfunction) might be induced by acidosis [41–43]. Furthermore, acidosis can cause cardiomyocytes to undergo apoptosis via caspase-12/caspase-3 activation (by endoplasmic reticulum (ER) stress, Ca^{2+} leakage) or the mediating effect of BNIP3 (Bcl-2 family) [44–46]. Since glutamine has been demonstrated to have a treatment effect on ER stress [47, 48], we suspect that the post-cardiac arrest acidosis-induced cardiomyocyte apoptosis could be improved by early glutamine administration.

Finally, although several studies reported that glutamine might recover the contractile function of the heart following ischemia/reperfusion injury [49, 50], the treatment effect on cardiomyocytes at a low pH level was still not clear. In the present study, we found that the beating function of cardiomyocytes was obviously increased following treatment with glutamine, especially at a low pH level. We suspected that the reasons for this finding might be cell stress (acid stress, with more acid leading to more stress) and a potential recovery effect on cardiomyocytes at a low pH level.

5. Limitations

There were certain limitations to this study. Firstly, the causes of post-cardiac arrest acidosis are complex, and the detailed mechanisms involved were not analyzed in this study. Secondly, the only recorded outcomes for the rats that achieved sustained ROSC were the rate of sustained ROSC and the duration of survival; neurologic evaluations were not performed. Thirdly, although glutamine was demonstrated to reduce ER stress and injury to cardiomyocytes presenting cell apoptosis, the detailed mechanisms involved were not clarified. Finally, hypoxia was not considered in the cell model analysis.

6. Conclusion

In conclusion, early administration of glutamine increased the duration of survival in the animal model of post-cardiac arrest acidosis. More importantly, glutamine decreased cardiomyocyte apoptosis and increased these cells' beating function at a low pH level.

Competing Interests

The authors report no conflict of interests related to this study.

Authors' Contributions

Yan-Ren Lin, Wen-Liang Chen, and Huai-En Lu conceived the study. Yan-Ren Lin and Wen-Liang Chen supervised the data collection. Chao-Jui Li, Shih-Han Syu, Cheng-Hao Wen, and Waradee Buddhakosai performed the experiments and data quality control. Han-Ping Wu, Huai-En Lu, Cheng Hsu Chen, and Yan-Ren Lin provided statistical advice and analyzed the data. Yan-Ren Lin and Wen-Liang Chen chaired the data oversight committee. Yan-Ren Lin drafted the manuscript, and all of the authors contributed substantially to its revision. Wen-Liang Chen and Huai-En Lu bear responsibility for the paper in its entirety.

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