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Resuscitation for Cardiac Arrest and Postcardiac Arrest Care

Lead Guest Editor: Yan-Ren Lin
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Editorial Board

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Editorial

Resuscitation for Cardiac Arrest and Postcardiac Arrest Care

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A well-coordinated team, both in prehospital and in-hospital resuscitation, will save lives. For example, high performance cardiopulmonary resuscitation (HPCPR) and extracorporeal cardiopulmonary resuscitation (ECPR), which were both established by closely coordinated teamwork, were recently demonstrated to shorten interruptive time of chest compression and reduce the postcardiac arrest syndrome, respectively [1–4]. Some leading councils (i.e., American Heart Association (AHA) and European Resuscitation Council (ERC)) pointed out the importance of group monitoring in performing resuscitation and emphasized the quality of postcardiac arrest care. Recently, AHA revised the golden guidelines for cardiac arrest resuscitation and postcardiac arrest care on January 2, 2018 [5]. Several leading journals also recently discussed how to increase the quality and outcome in the postcardiac arrest care (including strategic application of ECPR and hypothermia in treating pediatric or traumatic patients), thus making this topic hot and timely [1, 4, 6, 7]. The updated knowledge globally guides the treatment strategies of critical and emergency care. All new guidelines and knowledge can be clinically applied, challenged, and improved upon. In this special issue, we would like to provide an opportunity to introduce various related works discussing resuscitation for cardiac arrest and postcardiac arrest care.

In the field of oxygenation and cardiopulmonary resuscitation (CPR) or respiratory failure, Lee et al. introduced an animal study and demonstrated that continuous flow insufflation of oxygen using a one-way valve resulted in a greater level of oxygenation and less lung and brain injuries than intermittent positive pressure ventilation. Huang et al. performed a meta-analysis study and concluded that administering of high-flow nasal cannula therapy in the emergency department (ED) for respiratory failure patients might decrease the intubation rate compared with conventional oxygen therapy. Cho et al. investigated whether those capnometer readings could be easily affected by fluid exposure during treatment of critically ill patients. They prospectively compared the differences of the $ETCO_2$ level between proximal or distal connecting direct connect catheter mount (DCCM) and found that application of DCCM onto the capnometer setting seems to be effective in reducing capnometer malfunctioning under fluid exposing conditions. Lee et al. investigated three-dimensional shapes and deformability of red blood cells (RBCs) during and after asphyxia cardiac arrest in rats. In their study, quantitative phase imaging results revealed that RBC membrane fluctuations, sphericity, and surface area did not change significantly during CPR or after return of spontaneous circulation (ROSC) compared with initial values.

Second, the association between definitive airway establishment and outcomes of patients were also discussed in this special issue. Choi et al. reported that the mean intubation time was significantly shorter in using I-gel blind intubation than using I-gel bronchoscopic intubation or Macintosh laryngoscope.

The other studies focused on the short/long-term outcomes of out-of-hospital cardiac arrest (OHCA) patients.

Hsu Chen et al. analyzed the risk of new-onset heart failure of 49,101 nontraumatic OHCA adult patients. They found that, in patients aged from 61 to 75 years, a history of myocardial infarction or cardiomyopathy, and ischemic heart disease or infection as comorbidities, occurring during hospitalization were strong risk factors for new-onset heart failure. However, extracorporeal membrane oxygenation could decrease this risk. Most heart failure events occurred within 60 days after OHCA. For young traumatic OHCA patients, Huang et al. pointed out that Injury Severity Score, Glasgow Coma Scale, and Revised Trauma Score were all associated with increased mortality, prolonged intensive care unit stay, and longer length of hospital stay. Kim et al. administered the Mini-Mental State Examination (MMSE) to 92 cardiac arrest survivors who were treated with targeted temperature management immediately after regaining consciousness. Cognitive impairments were common immediately after patients regained consciousness but recovered substantially before intensive care unit discharge. Moreover, they also reported hypoalbuminemia was common after cardiac arrest, and the serum albumin level at admission was associated with poor neurological outcomes at 6 months after cardiac arrest in patients treated with targeted temperature management. Choi et al. analyzed 6,335 OHCA patients. They found that both the EMS response times to OHCA events in high-rise buildings and the probability of a neurologically favorable discharge differed obviously between homes and public places. The prognosis of an OHCA patient was more likely to be affected by the building structure and use rather than the floor height.

This special issue highlights several articles that report improvements in OHCA-related oxygenation, airway management, resuscitation strategies, and outcomes. We strongly believe that readers will gain useful information from this issue.

Conflicts of Interest

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

Acknowledgments

The editors appreciate all authors who made contribution for this special issue. They hope this collection of articles will be useful to the scientific community.

Yan-Ren Lin
Aristomenis K. Exadaktylos
Kee-Chong Ng
John M. Ryan

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Research Article

The Effect of a Modified Constant Flow Insufflation of Oxygen during Cardiopulmonary Resuscitation in a Rat Model of Respiratory Cardiac Arrest on Arterial Oxygenation, Alveolar Barotrauma, and Brain Tissue Injury

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Aim. Intermittent positive pressure ventilation (IPPV) can adversely affect cardiopulmonary resuscitation outcomes by increasing the intrathoracic pressure. Continuous flow insufflation of oxygen (CFIO) has been investigated as a potential alternative, but evidence supporting its superiority over intermittent positive pressure ventilation in cases of cardiac arrest is scant. The aim of the current study was to compare the effects of continuous flow insufflation of oxygen using a one-way valve during cardiopulmonary-resuscitation with intermittent positive pressure ventilation in a rat model of respiratory arrest. *Methods*. Male Sprague-Dawley rats weighing 400~450 g (from minimum to maximum) were randomly assigned to either a sham, IPPV, or CFIO group ($n = 10$ per group). Respiratory arrest was induced by blocking the endotracheal tube. Arterial blood gas analysis was performed during cardiopulmonary resuscitation to compare the oxygenation levels. Tissues were then harvested to compare the degrees of pulmonary barotrauma and ischemic brain injury. *Results*. Return of spontaneous circulation was observed in 6/10 rats in the IPPV group and 5/10 in the CFIO group. During cardiopulmonary resuscitation, the mean PaO_2 was significantly higher in the CFIO group (83.10 mmHg) than in the IPPV group (56.10 mmHg). Lung biopsy revealed more inflammatory cells and marked thickening of the alveolar wall in the IPPV group; the group also exhibited a higher frequency of neuroglial cells and apoptotic bodies of pyramidal cells, resulting from ischemic injury. *Conclusion*. In a rat model of respiratory arrest, CFIO using a one-way valve resulted in a greater level of oxygenation and less lung and brain injuries than with IPPV.

1. Introduction

A cardiopulmonary resuscitation (CPR) team performs positive pressure ventilation (PPV) using a bag-valve-mask, supraglottic airway, or endotracheal intubation combined with chest compression in cases of prehospital or in-hospital cardiac arrest (CA). During CPR, there must be sufficient venous return to allow ventricular filling during the relaxation phase to effect an adequate outflow during the active compression phase. However, although PPV may be an

appropriate CPR technique, it may hinder venous return because it increases the ITP. Thus, inappropriate PPV may impair the quality of CPR [1].

Multiple studies have been conducted to resolve this problem. Kill et al. [2] introduced a method of synchronizing chest decompression and ventilation and reported that high oxygenation was achieved with this method in a porcine model of CA. Devices inhibiting the inspiration trigger during chest decompression, such as inspiratory impedance threshold device (ITD) and the Boussignac cardiac arrest resuscitation device (B-card), have also been investigated [3]. However, because the ITD still use a PPV technique. Also, in the B-card using the CFIO method, collision of oxygen inflow and exchanged gas outflow make pressure. This pressure can influence venous return and alveoli. Finally, brain injury caused by reduced brain blood flow might be a possibility due to reduced venous return, as well as reduced oxygen supply and increased ITP, causing pulmonary barotrauma.

In 2000, Saissy et al. [4] reported that the effects of continuous flow insufflation of oxygen (CFIO) were comparable to those achieved by intermittent positive pressure ventilation (IPPV) in cases of prehospital CA. In a study reported in 2004, investigating the application of CFIO and IPPV with endotracheal intubation in a porcine model of ventricular fibrillation (VF) CA, Steen et al. [5] reported that oxygenation and coronary perfusion pressure were significantly higher in the CFIO group.

In 2006, Bertrand et al. [6] reported that it is possible to deliver oxygen during CPR using CFIO in patients who have experienced prehospital CA. In a study involving patients with witnessed VF CA, Bobrow et al. [7] reported that patients who were delivered oxygen via CFIO were significantly more likely to survive and get discharged and exhibited better neurologic outcomes than patients who received PPV.

Notably, however, none of the above-menti–oned previous studies investigated whether CFIO could be applied in cases of respiratory CA. We hypothesized that CFIO using a one-way valve connected to an opening channel would be able to improve oxygenation than conventional IPPV, which would reduce ischemic brain injuries and pulmonary barotrauma. This hypothesis was investigated in the current study by comparing the effects of CFIO using a one-way valve, expected to reduce ITP during CPR, with conventional IPPV in a rat model of respiratory CA caused by oxygenation failure.

2. Methods

2.1. Study Design. This prospective randomized longitudinal rat study was approved by the institutional animal care and use committee at Hanyang University, South Korea (approval number 2016-0075A). The study was conducted at the Animal Study Laboratory of Hanyang University School of Medicine using Sprague-Dawley rats weighing 400–450 g. The rats had access to standard food and water ad libitum, and they were acclimatized to the environment for several days before the experiment. Cages were managed in accordance with the National Research Council standards.

2.2. Sample Size. The sample size was calculated based on the PCO_2 levels of the IPPV and CFIO groups in the pilot study (PCO_2 levels: IPPV group, 89.95 (86.70–91.63) mmHg and CFIO group, 99.90 (97.98–103.00) mmHg). The minimum sample size was 5 in each group, and an analysis with G-power 3.1.2® (Heine Heinrich University, Düsseldorf, Germany) with a 0.05 error level and 0.95 power was performed. The dropout rate was 30%, which accounted for the rats that were excluded from the experiment or could affect the experimental results before the end of the experimental protocol. The survival rate was estimated to be 50~70% considering the histological examination of the surviving rats after CPR. Therefore, the final sample size was calculated as 10 rats for each group. When a rat died during preparation for the experiment or when serious problems arose that could affect the outcomes of the experiment, the rat was excluded from the experimental results.

2.3. Animal Study Protocol. During experiments, the temperature and humidity of the laboratory were consistently maintained at 24°C and 35%, respectively. To maintain body temperature, a surgical lamp was applied throughout all experiments, and the core temperature of all rats was maintained between 36°C and 37°C, the normal body temperature of rats. The rats were randomly divided into sham, IPPV, and CFIO groups via a computer program. Invasive blood pressure monitoring was performed in all rats via a femoral artery catheter while each rat was connected to a ventilator after the induction of deep anaesthesia via isoflurane with intramuscular injection of a mixture of Zoletil® (Virbac, Carros, France, zolazepam + ketamine, 30 mg/kg) and Rompun® (Bayel, Leverkusen, Germany, xylazine, 10 mg/kg) in a 2 : 1 ratio. The femoral artery catheter was also used for arterial blood gas analysis (ABGA). In the IPPV and CFIO groups, an intravenous line was inserted into the tail vein for epinephrine infusion during CPR.

Before inducing respiratory CA, 0.3 cc of arterial blood was collected from each rat to compare the baseline characteristics on ABGA among the three groups. After the ABGA in the sham group, while maintaining artificial ventilation, the 24 G catheter was removed from the femoral artery, and when the rats had recovered adequate spontaneous breathing, they were taken off the ventilator and placed in a new cage lined with warm cotton.

With reference to the respiratory CA model reported by Bai et al. [8] in 2015, the point of CA was set to the moment at which the mean arterial pressure dipped below 20 mmHg from 8 min after blocking of the endotracheal tube [3–6]. From this point, chest compression was begun at 200 pm for 2 min using metronome feedback, and one epinephrine dose (30 μg/kg) was injected through the intravenous line. ROSC was checked after 2 min of chest compression. ROSC was determined based on a heart rate exceeding 200 bpm, palpation of the apical pulse, and invasive arterial blood pressure monitoring. Successful resuscitation was defined as ROSC that persisted for more than 10 min [9–13].

During CPR, the IPPV group was put on PPV using a ventilator for rodents, and the CFIO group was administered oxygen via an endotracheal tube connected to a one-way valve (see Figure 1).

IPPV during CPR: using a rodent ventilator, the Inspira Advanced Safety Ventilator (HARVARD APPARATUS, Holliston, MA, USA) was set to provide one positive pressure breath with a tidal volume of 8 mL/kg animal weight for every four compressions (50 breaths/min).

CFIO during CPR: using a novel one-way valve connected with an opening channel, oxygen flow was provided through the gas inlet at 200 ml/kg/min to the one-way valve and to the endotracheal tube. During chest compression, gas from the lungs passes through the opening channel and opens the one-way valve. During chest decompression, oxygen flows and fills in the opening channel to the endotracheal tube and to all lung fields (see Figure 1).

After 1 min of CPR, a 0.3-cc arterial blood sample was taken for ABGA to compare the levels of oxygenation associated with the different ventilation methods. During CPR, isoflurane was not administered and the two groups received oxygen only.

In successfully resuscitated rats, oxygen supply through the ventilator was resumed and ventilator care was restarted. Rats that exhibited ROSC were taken off the ventilator and moved to a new cage (see Figure 2). At 24 and 48 hours after resuscitation, quantitative neurologic assessments were performed with 21 items using the neurologic deficit score (NDS) system described by Jia et al. [14] (see Table 1).

2.4. Histologic Study Protocol. In accordance with the method described by Gage et al. [15], perfusion fixation was performed via intramuscular injection of Zoletil® and Rompun® in a 2 : 1 ratio 48 hours after resuscitation in a sedated state to prepare biopsy specimens. For lung biopsy, haematoxylin-eosin staining was performed. For brain biopsy, Nissl staining was performed to compare neuronal injuries.

2.5. Statistical Analysis. Test results were analysed using SPSS 21.0 software (IBM Analytics, IL, Chicago, USA). Although the results were normally distributed, the nonparametric Kruskal–Wallis test was used given the fact that there were 10 rats in each group. The sham group and two experimental groups were compared using the Kruskal–Wallis test. Pairwise comparisons were performed using the Mann–Whitney test with post hoc Bonferroni correction. From the total number of pyramidal cells observed at ×400 magnification in the Cornu-Ammonis 3 region of the hippocampus, which is vulnerable to hypoxic injuries, the percentages of stained apoptotic bodies and normal pyramidal cells were calculated for each slide six times for all rats. The results from the sham group were compared to those from the two experimental groups. As with the NDS, the percentages of all three groups were compared using the Kruskal–Wallis test, and paired comparisons (three comparisons) were performed using the Mann–Whitney test with post hoc Bonferroni correction ($p < 0.017$).

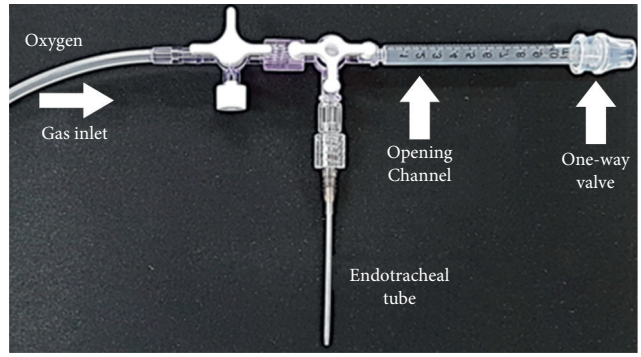

Figure 1: One-way valve with an opening channel.

3. Results

Respiratory CA was induced in all rats of the two experimental groups, and 11 rats regained spontaneous circulation after CPR. Six of ten rats were in the IPPV group, and five of ten rats were in the CFIO group.

3.1. Baseline Characteristics of Each Group. There was no significant difference in body weight between the sham group (418.60 ± 2.55 g) and the two experimental groups (IPPV 417.30 ± 4.64 g, CFIO 417.90 ± 3.96 g). There was no significant difference in the time to respiratory CA between the IPPV group (500.90 ± 10.83 sec) and CFIO group (503.00 ± 10.08 sec), and there were no significant differences in the ABGA results (pH, $PaCO_2$, PaO_2, HCO_3^-, base excess, and lactate) before CA in these two groups (see Table 2).

3.2. Results of ABGA Performed during CPR. There were no significant differences in the arterial blood pH, HCO_3^-, base excess, or lactate during CPR between the two experimental groups ($p > 0.05$ for all). However, the CFIO group had significantly higher $PaCO_2$ (99.90 mmHg) and PaO_2 (83.10 mmHg) than the IPPV group ($PaCO_2$ 89.95 mmHg, PaO_2 56.10 mmHg; $p < 0.001$ for both comparisons) (see Table 3).

3.3. Neurologic Outcome Assessment. NDS 24 hours after ROSC was 70 in the IPPV group, which was significantly lower than that in the sham (80; $p < 0.001$) and CFIO (76; $p = 0.004$) groups; however, the sham group did not differ significantly from the CFIO group ($p = 0.081$). NDS 48 hours after ROSC was 74 in the IPPV group, which was significantly lower than that in the sham (80; $p < 0.001$) and CFIO (78; $p = 0.001$) groups; however, the sham group did not differ significantly from the CFIO group ($p = 0.398$ (see Figure 3).

3.4. Lung Biopsy Results. Lung biopsy specimens were haematoxylin-eosin-stained for comparison. Compared with the sham group, the two experimental groups exhibited thickening of the alveolar wall, caused by barotrauma and

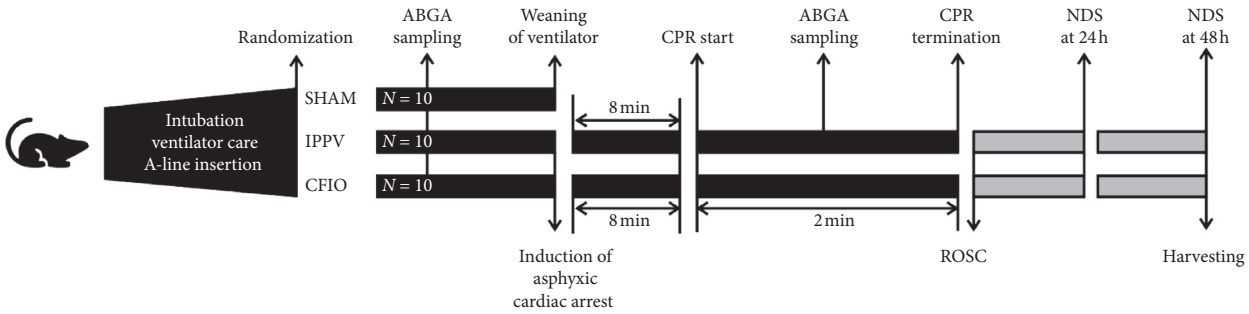

Figure 2: Animal study protocol. A-line, arterial line; IPPV, intermittent positive pressure ventilation; CFIO, continuous flow insufflation of oxygen; ABGA, arterial blood gas analysis; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; NDS, neurologic deficit score.

Table 1: Neurologic deficit scoring system.

Items (score)		Scoring system		
General behaviour deficit (0–19)	Consciousness	Normal (10)	Stupor (5)	Comatose (0)
	Arousal (eye opening)	Spontaneous (3)	Pain (1)	No (0)
	Respiration	Normal (6)	Abnormal (3)	Absent (0)
Brain stem function (0–21)	Olfaction	Present (3)		Absent (0)
	Vision	Present (3)		Absent (0)
	Pupillary reflex	Present (3)		Absent (0)
	Corneal reflex	Present (3)		Absent (0)
	Startle reflex	Present (3)		Absent (0)
	Whisker stimulation	Present (3)		Absent (0)
	Swallowing	Present (3)		Absent (0)
Motor and sensory (0–12)	Strength, right	Normal (3)	Stiff/Weak (1)	Paralyzed (0)
	Strength, left	Normal (3)	Stiff/Weak (1)	Paralyzed (0)
	Pain withdrawal, right	Brisk (3)	Weak (1)	No (0)
	Pain withdrawal, left	Brisk (3)	Weak (1)	No (0)
Behaviour (0–18)	Gait coordination	Normal (3)	Abnormal (1)	Absent (0)
	Balance on beam	Normal (3)	Abnormal (1)	Absent (0)
	Righting reflex	Normal (3)	Abnormal (1)	Absent (0)
	Negative geotaxis	Normal (3)	Abnormal (1)	Absent (0)
	Visual placing	Normal (3)	Abnormal (1)	Absent (0)
	Turning alley	Normal (3)	Abnormal (1)	Absent (0)
Seizures (0–10)	Seizures	No (10)	Focal (5)	General (0)

Table 2: Baseline characteristics of the experimental rats, all of which were male and approximately 15 weeks old.

Age Sex	Sham ($n = 10$)	Group IPPV ($n = 10$) 15 weeks old Male	Group CFIO ($n = 10$)	p value
Weight, g	419.00 (415.75–421.00)	417.50 (413.25–421.25)	418.00 (414.50–421.25)	0.86
Arrest induction time, s	NA	499.50 (491.25–510.00)	500.00 (495.75–508.00)	0.66
pH	7.32 (7.29–7.34)	7.33 (7.31–7.35)	7.32 (7.29–7.34)	0.79
PCO_2	32.00 (30.25–33.78)	31.55 (30.25–34.43)	30.15 (29.63–32.13)	0.19
PO_2	121.15 (119.18–125.45)	121.70 (116.85–127.68)	120.65 (118.95–125.65)	0.98
HCO_3^-	30.10 (29.33–30.90)	29.65 (28.98–30.23)	29.10 (28.60–29.65)	0.31
Base excess	−1.55 (−1.8–−1.2)	−1.3 (−1.93–1.08)	−.3 (−1.43–−1.18)	0.67
Lactate	2.00 (1.78–2.10)	2.10 (2.00–2.30)	2.05 (1.98–2.13)	0.31

Kruskal-Wallis analysis, median (IQR), $p < 0.05$ was considered statistically significant. IPPV, intermittent positive pressure ventilation; CFIO, continuous flow insufflation of oxygen; NA, not applicable.

multiple inflammatory cells. Most cells were macrophages and were observed in the thickened alveolar wall and inside the alveoli. These observations were more marked in the lung samples of the IPPV group than in the CFIO group (see Figure 4).

3.5. Brain Biopsy Results. In the Nissl-stained brain tissue specimens, the IPPV group exhibited a higher percentage of apoptotic pyramidal bodies caused by ischemic injuries and an elevated count of neuroglial cells, which respond to nerve injuries, compared with the CFIO group (Figure 5(a)).

Table 3: Comparisons of arterial blood gas parameters in two experimental groups 1 min after the start of cardiopulmonary resuscitation in a rat model of respiratory arrest.

	IPPV group	CFIO group	p value
pH	7.01 (6.98–7.05)	6.99 (6.97–7.00)	0.06
$^{*}PCO_2$	89.95 (86.70–91.63)	99.90 (97.98–103.00)	<0.001
$^{*}O_2$	56.10 (54.68–58.25)	83.10 (81.05–87.50)	<0.001
HCO_3-	23.90 (22.58–24.95)	24.10 (23.10–24.98)	0.59
Base excess	−4.70 (−6.35–−4.15)	−4.40 (−5.13–−4.08)	0.40
Lactate	4.55 (4.10–5.10)	4.85 (4.30–5.15)	0.45

Mann–Whitney test, median (IQR), $p < 0.05$ was considered statistically significant. *Statistical significant. ABGA, arterial blood gas analysis; CPR, cardiopulmonary resuscitation; IPPV, intermittent positive pressure ventilation; CFIO, continuous flow insufflation of oxygen.

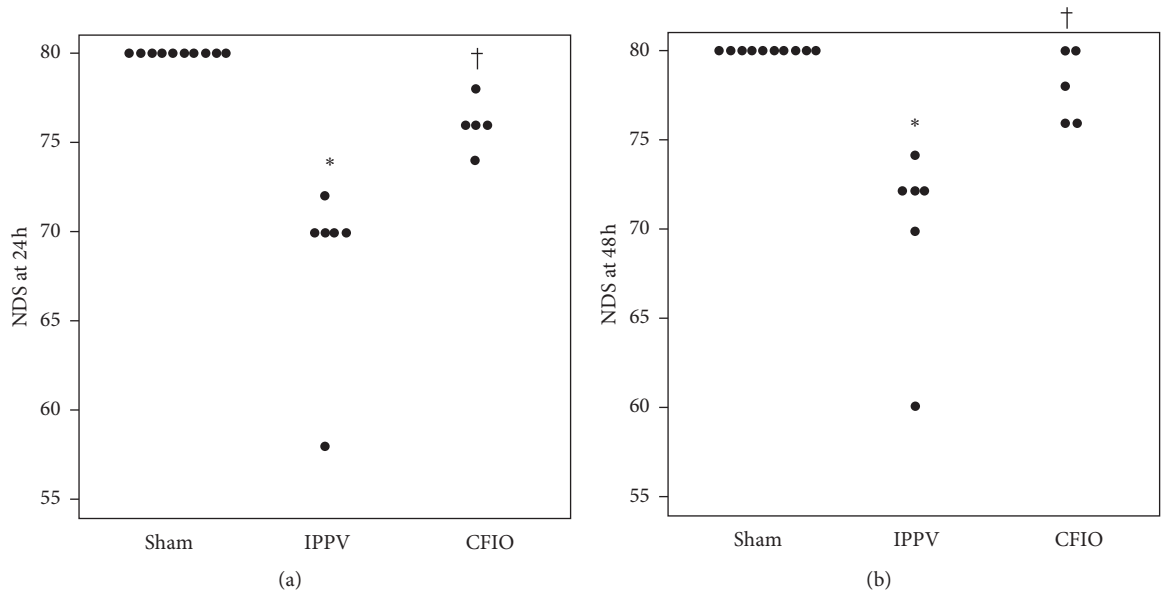

Figure 3: Neurologic deficit scores 24 hours (a) and 48 hours (b) after the return of spontaneous circulation in a rat model of respiratory arrest. Sham group ($n = 10$), IPPV group ($n = 6$), CFIO group ($n = 5$), and $^{*}p < 0.01$ compared to the sham group; $^{\dagger}p < 0.017$ compared to the IPPV group. NDS, neurologic deficit score; IPPV, intermittent positive pressure ventilation; CFIO, continuous flow insufflation of oxygen.

3.6. Percentage of Ischemic Injured Brain Cells and Normal Pyramidal Bodies. The percentages of apoptotic bodies caused by ischemic injury in each group were calculated and compared. In the sham group, these percentages were significantly lower than they were in both the IPPV group (41.01 ± 4.62, $p < 0.001$) and the CFIO group (12.73 ± 2.09, $p < 0.001$), and the percentages in the CFIO group were significantly lower than those in the IPPV group ($p < 0.001$) (Figure 5(b)).

4. Discussion

The major findings of the current study were that the CFIO method using a one-way valve connected to an opening channel led to a greater level of oxygenation and lower pulmonary barotrauma and hypoxic brain injury than those produced by the conventionally recommended IPPV method in a rat model of respiratory CA.

Research on the possibility of delivering oxygen via CFIO began in the 1980s. In 1982, Lehnert et al. [16] first reported the possibility of oxygenation via CFIO in a canine apnoea model. In 1991, Brochard et al. [17] reported that CFIO may be used in limited situations wherein the patient must be taken off artificial respiration, such as during suctioning through an endotracheal tube. In 2004, Meggs et al. [18] reported that pigs in a porcine apnoea model were able to survive without respiratory effort for an average of 75 min while CFIO was maintained. Several subsequent studies investigating the feasibility of CFIO in CPR followed on the basis of these initial studies [4–7].

In a study on prehospital CA patients published in 2000, Saissy et al. [4] reported that CFIO yielded comparable effects to those of IPPV, as indicated by significantly similar ABGA results associated with the two methods. However, ABGA was performed after ROSC in that study; therefore, the parameters were not accurate representations of oxygenation during CPR. Furthermore, the study did not analyse differences in brain or lung injuries or neurologic outcomes associated with each method of ventilation.

In 2004, Steen et al. [5] reported that CFIO led to a significantly higher level of oxygenation and higher coronary perfusion pressure than IPPV in a porcine model of VF CA, but the study was limited to VF CA induced in a sufficiently oxygenated state and did not analyse hypoxic brain injuries

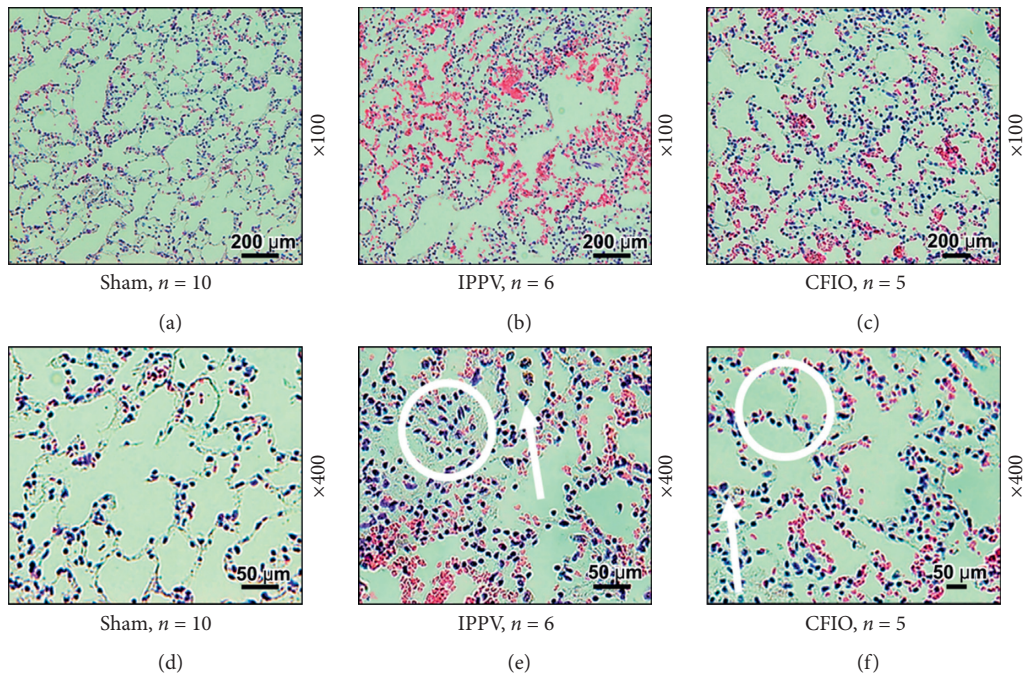

Figure 4: Histologic staining of lung tissue with haematoxylin-eosin 48 hours after the return of spontaneous circulation. Alveolar wall thickening was greater in the IPPV group than in the CFIO group, and there were more inflammatory cells. White arrows are pointing at inflammatory cells, and white circles indicate thickening of the alveolar wall. IPPV, intermittent positive pressure ventilation; CFIO, continuous flow insufflation of oxygen.

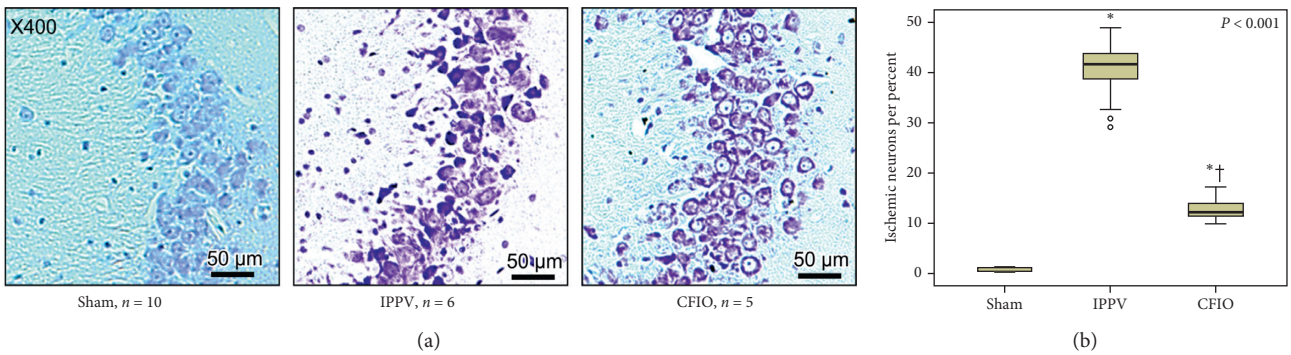

Figure 5: Histologic examination of hippocampal Cornu-Ammonis 3 regions with cresyl violet staining 48 hours after the return of spontaneous circulation. (a) Representative images of cresyl violet staining at 400 × magnification. There were more apoptotic pyramidal cells and neuroglial cells in the IPPV group than in the CFIO group. (b) Boxplots representing the proportions of ischemic neurons per total number of neurons. $^{*}p < 0.001$ compared to the sham group; $^{\dagger}p < 0.001$ compared to the IPPV group. IPPV, intermittent positive pressure ventilation; CFIO, continuous flow insufflation of oxygen.

or differences in lung barotrauma or oxygenation between the ventilation methods.

In 2006, Bertrand et al. [6] reported that CFIO delivered sufficient oxygen in patients with prehospital CA, but they also reported that the patients had poor outcomes. Notably, however, the grounds for claiming that a higher level of oxygenation was induced by CFIO in that study was that there was a significantly higher number of patients with oxygen saturation of greater than 70% during CPR in the CFIO group, as opposed to measuring oxygen partial pressure—an index for oxygenation—via ABGA during CPR. Furthermore, although differences between the thoracic injuries associated with the two ventilation methods were investigated in that study, it was simply stated that the incidence of rib fracture was higher in the IPPV group than in the CFIO group. Pulmonary barotrauma was not evaluated via biopsy. On the basis of this additional finding, Bertrand et al. [6] speculated that PPV would increase ITP, and when combined with the elevated pressure caused by chest compression, it may increase the risk of rib fracture.

In 2009, Bobrow et al. [7] compared patients with witnessed prehospital VF CA who were either provided oxygen via a mask or administered PPV using a bag valve mask and reported that the former group had better

neurologic outcomes. However, that study was limited, in that it involved VF, in which chest compression and defibrillation are more important than oxygenation.

These abovementioned studies evaluating the effects of CFIO [4–7] were focused on human patients or animal models of VF CA, in which the importance of oxygenation is relatively lower than it is for respiratory CA. Moreover, the CFIO methods used in these studies involved the delivery of oxygen using multiple channels or via a general endotracheal tube or mask. In contrast, the present study utilized a modified CFIO technique in which the inspiratory flow into the endotracheal tube is strengthened by closing the valve to allow oxygen accumulation in the opening channel of the tube. The valve is then opened in response to elevated pressure in the opening channel during chest compression, so as not to increase ITP. Furthermore, the present study utilized a rat model of respiratory CA such that oxygenation is important for recovery. The oxygenation effects of two different ventilation methods were investigated by performing ABGA during CPR. And an alveolar barotrauma and hypoxic brain injury associated with the two methods also were assessed via histological evaluation of lung and brain biopsy from survived rats.

Although the current study used a rat respiratory CA model, oxygenation during CPR was significantly higher in the CFIO group than in the IPPV group, which is similar to previous results derived from VF patients and animal models [4–7]. Haemodynamic indicators such as cardiac output could not be measured in the current study because we used rats rather than pigs, but the associated findings were the same in both studies.

In the present study, for the CFIO method, an endotracheal tube connected to a one-way valve and an opening channel were utilized. This new CFIO method was designed such that endotracheal inspiratory flow is strengthened during chest decompression by the oxygen accumulated in the opening channel as a result of the closed valve. Furthermore, during chest compression, there is no collision between oxygen flowing toward the valve and gas being pushed out because the valve is not directly located within the channel connected to the trachea. Instead, the outflow of gas from the airway is actually promoted because the valve is opened due to the pressure in the opening channel, and the oxygen flow is directed toward the valve. These features are thought to reduce ITP, and consequently, the CFIO group exhibited less severe alveolar damage and hypoxic brain injury compared with the IPPV group.

The current study has some limitations. First, the body temperatures of the surviving rats were not monitored after they were placed back into a cage. Rats tend to exhibit spontaneous reduction in body temperature when recovering from CA [10], but the consequent effects were not considered in the present study. Second, respiratory CA was induced while providing 100% oxygen, so the models utilized may differ from real-life respiratory CA occurring amid exposure to 21% oxygen, the oxygen concentration in normal air. Third, CPR was only performed for 2 min after the induction of CA, in an attempt to eliminate the effects of the duration of CPR while investigating differences in pulmonary and brain tissue injuries according to the ventilation method. This may have affected the histological outcomes. Fourth, we did not check the airway pressure during CPR in each group. A continuous flow of oxygen toward the lower airway is likely to create a positive pressure. According to the study by Steen et al. (2004), the CFIO group performed better in terms of oxygenation than the IPPV group, but a higher airway pressure during CPR was reported than the IPPV group. This may be due to a positive pressure created by the continuous flow of oxygen toward the lower airway. And they did not use one-way valves, nor did they use opening channels to control the tidal volume induced during decompression. However, in this study, the CFIO group showed less damage due to pressure, according to alveolar histological findings. Further studies are needed to clarify the above findings, and we aim to conduct a large animal experiment in the future. Finally, the study used rat models, so the results cannot be directly extrapolated to humans. The results of the study are similar to those of some previous human studies [4–7]; however, they shed light on the potential usefulness of CFIO incorporating a one-way valve with an opening channel during CPR by comparing the brain and lung biopsy results associated with different ventilation methods.

Additional large animal studies are needed to compare the haemodynamic outcomes of three different ventilation methods using the inspiratory ITD, B-card, including the device used in the present study. Such studies may facilitate the development of new artificial ventilation methods or devices that address the problems associated with the long-recommended IPPV method during CPR, e.g., the need for a person to be in charge of ventilation during CPR, possibility of tissue damage caused by PPV, and reduced quality of CPR due to PPV.

5. Conclusion

In a rat model of respiratory CA, the CFIO method using a one-way valve designed to lower ITP during CPR resulted in a higher level of oxygenation with lower incidences of lung and brain injuries compared with the IPPV method. These protective effects on the lung and brain may be associated with the one-way valve, which was designed to induce a greater reduction in barotrauma of the lung and result in higher oxygenation than that in the IPPV method.

Data Availability

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

Disclosure

This study has been presented in abstract form at the Annual international Conference of European Resuscitation Congress, Bologna, Italy, on September 22, 2018.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Authors' Contributions

Y Lee and S Lee contributed equally to this study. Y Lee and S Lee designed and mainly conducted this study. HJ Choi supervised the overall data collection process, had full access to all the data in the study, and assumed responsibility for the integrity of the data. S Lee blindly performed the NDS assessment and the data analysis. S Hwang and J Park blindly conducted the histopathological examinations. Y Lee wrote the initial draft of the article. All the authors extensively reviewed the final version of the article and provided feedback.

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Research Article

The Impact of Emergency Interventions and Patient Characteristics on the Risk of Heart Failure in Patients with Nontraumatic OHCA

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Background. Since out-of-hospital cardiac arrest- (OHCA-) related dysfunction (ischemic/reperfusion injury and inflammatory response) might result in long-term impairment, we suspect that new-onset heart failure might be common in long-term survivors. However, these relationships had not been well addressed, and we aimed to analyze the impact of emergency interventions and patient characteristics on the risk of new-onset heart failure in patients with nontraumatic OHCA. *Methods*. The Taiwanese government healthcare database contains data for 49,101 nontraumatic OHCA adult patients from 2011-2012, which were analyzed in this study. Nontraumatic OHCA patients who survived to the intensive care unit (ICU) were included as the study group ($n = 7{,}321$). Matched patients ($n = 21{,}963$) were recruited as a comparison group. Patients with any history of heart failure or cardiac arrest were not included in either group. All patients were followed-up for 6 months for the identification of new-onset heart failure. Adjustments were made for demographics, age, emergency interventions, and comorbidities as potential risk factors. *Results*. In all, 3.84% ($n = 281$) of OHCA patients suffered new-onset heart failure, while only 1.24% ($n = 272$) of matched patients in the comparison group suffered new-onset heart failure. Strong risk factors for heart failure were age (60–75 years, HR: 11.4; 95% CI: 9–14.4), medical history (myocardial infarction, HR: 2.47; 95% CI: 2.05–2.98 and cardiomyopathy, HR: 2.94; 95% CI: 1.45–5.94), and comorbidities during hospitalization (ischemic heart disease, HR: 4.5; 95% CI: 3.46–5.86). Only extracorporeal membrane oxygenation (ECMO) decreased the risk of heart failure. Most (53.6%) heart failure events occurred within 60 days after OHCA. *Conclusion*. An age from 61 to 75 years, a history of myocardial infarction or cardiomyopathy, and ischemic heart disease or infection as comorbidities occurring during hospitalization were strong risk factors for new-onset heart failure in OHCA patients. However, ECMO could decrease this risk. More importantly, most heart failure events occurred within 60 days after OHCA.

1. Introduction

Although some nontraumatic out-of-hospital cardiac arrest (OHCA) patients can initially achieve restoration of spontaneous circulation (ROSC) after resuscitation, the overall survival rate of OHCA ranges only from 5.7% to 8.3% [1–4]. Even among OHCA patients discharged from the hospital, the one-year survival rate is only from 7.7% to 11.5% [1–3,5]. Some major risk factors, including unhealed underlying diseases, arrest-related hypoxia injury, and new-onset postresuscitation comorbidities, are considered to be responsible for this poor outcome [6–8]. Furthermore, new-onset postresuscitation comorbidities, which might interact with essential diseases or cause sickness independently, can be life-threatening and difficult to prevent [9–14].

Among such postresuscitation comorbidities, new-onset heart failure might be the most important factor associated with the cardiopulmonary function and hemodynamics of OHCA patients [8]. Diseases of cardiac origin (i.e., acute coronary syndrome and cardiac arrhythmia) are some of the most common etiologies of OHCA (accounting for 60% to 70%); myocardial dysfunction is also common (up to 66%) during the early postresuscitation period [15, 16]. Therefore, we suspect that new-onset heart failure might be very predominant among OHCA survivors. Although a few animal studies have tried to identify the risk factors (including ischemia/reperfusion injury, systemic inflammatory response, and catecholamine surge) of postresuscitation heart failure in humans, this information has not been well addressed, and there is a lack of relevant long-term follow-up investigations [12, 17, 18]. Since some causes of this dysfunction (I/R injury, inflammatory response) might result in long-term impairment, we suspect that new-onset heart failure might be common in long-term survivors. More importantly, cardiac arrest-related complications and emergency interventions might also influence the occurrence of heart failure. However, these relationships had not been well addressed before this large population study. In this study, we aimed to analyze the impact of emergency interventions and patient characteristics on the risk of new-onset heart failure in patients with nontraumatic OHCA.

2. Methods and Materials

2.1. Data Source. Taiwan's Ministry of Health and Welfare (MOHW) established a Health and Welfare Data Center (HWDC), a data repository site that centralizes the NHIRD and about 70 other health-related databases for data management and analyses. The data that we used were obtained from the Taiwan's National Health Insurance Research Database (NHIRD). This program is centralized by the Health and Welfare Data Center (HWDC) and supported by the Taiwan's Ministry of Health and Welfare (MOHW). The NHIRD covers over 99% of Taiwan's population (over 22 million people). With the MOHW's permission, data from the NHIRD could be extracted and analyzed for the purpose of scientific research.

2.2. Ethical Approval

2.2.1. Institutional Review Board (IRB) Permission. The protocol of this study was reviewed and approved by the IRB of Changhua Christian Hospital (permission code: 150117). To ensure that the data extracted from the NHIRD were used only for scientific research, our protocol, IRB permission, and output data were all supervised by the Taiwanese government.

2.2.2. Patient Privacy Policy. To protect personal privacy, all patients' medical records were secondary data (deidentified). Moreover, the data were not allowed to be displayed if the specific search parameters yielded fewer than 3 patients (identification possible).

2.3. Study Setting and Population. This was a retrospective cohort study. The study and comparison groups comprised patients with database records during the study period (January 2011 to December 2012). The selection flowchart is shown in Figure 1. All patients were followed-up for 6 months for the identification of those who suffered new-onset heart failure. In addition, the demographics, medical histories, emergency interventions, and comorbidities were analyzed according to three age groups (<60 years, 60–75 years, and >75 years) for the risk evaluation.

2.3.1. Inclusion Criteria

(1) Definition of Study Group. Patients who met all of the following characteristics during the study period were included in the study group:

(1) Patients had experienced their first nontraumatic OHCA and were diagnosed by emergency department (ED) physicians, with OHCA defined using the International Classification of Diseases, 9th revision, clinical modification (ICD-9-CM) codes 798–799 and 427.5

(2) Patients had ever received resuscitation in the ED and survived to intensive care unit (ICU) admission

(2) Definition of Comparison Group. Patients in this group were randomly selected from the remaining patients in the NHIRD. They were matched to patients in the study group in terms of age, sex, and follow-up period. Three times as many patients were included in this group than in the study group.

(3) Definition of Primary Outcome (New-Onset Heart Failure). New-onset heart failure was diagnosed according to the ICD-9-CM code 428.X.

2.3.2. Exclusion Criteria. Patients with the following conditions were excluded from both groups:

(1) Patients with any history of heart failure or cardiac arrest (traumatic/nontraumatic) before the study began

(2) OHCA patients who did not receive post-resuscitation care or evaluations

(3) Pediatric patients (age <18 years)

(4) Patients with OHCA related to trauma (major diagnosis including the following ICD-9-CM codes: 800–809, 810–819, 820–829, 830–839, 850–854, 860–862, 863–869, 900–904, 925–929, 940–949, and 950–957)

(5) Patients with incomplete medical records

(6) Patients who terminated their insurance during the study period

2.4. Study Protocol. In all, 7,321 OHCA patients (surviving to ICU admission) were included in the study group, and 21,963 patients were included in the comparison group.

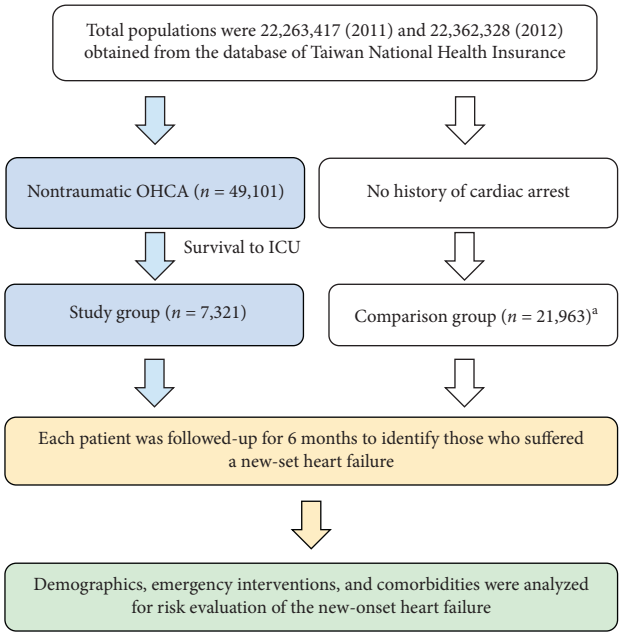

Figure 1: Selection flowchart of this study.

Among the study group, cardiac and noncardiac causing OHCA were identified. We followed-up all patients for 6 months to identify those who suffered new-onset heart failure. Moreover, this study considered and adjusted the hazard ratio (HR) depending on different variables between the two groups.

2.5. Data Analysis. Descriptive statistics, the Chi-squared test, the crude HR with Cox proportional hazards models, the log-rank test, and the Kaplan–Meier method were applied in this study. We used SAS (SAS Institute, Inc., Cary, NC, USA) to select patients. The SAS programming language and the results of the analysis were routinely checked by governmental database supervisors to ensure that all information was deidentified.

Descriptive statistics for independent variables were first determined. Demographics, including sex, age, economic level, geographic region and degree of residence urbanization, and medical history, including myocardial infarction, hypertension, diabetes mellitus, cardiomyopathy (congestive, constrictive, familial, idiopathic, infiltrative, obstructive, and nonspecific), chronic obstructive pulmonary disease (COPD) and asthma, chronic kidney disease (CKD), systemic lupus erythematosus (SLE), liver cirrhosis, atrial flutter/atrial fibrillation, sicca syndrome, and rheumatic arthritis, are reported as the number, percentage, or mean ± standard deviation (SD). Detailed information regarding how the economic levels, geographic regions, and degrees of urbanization were classified has been described in previous database studies [19, 20]. In addition, information on emergency interventions (for treating OHCA), including defibrillation, PCI, ECMO, and therapeutic hypothermia, are reported. New-onset comorbidities during hospitalization were mainly categorized as infection (i.e., respiratory tract infection, urinary tract infection, and septicemia), ischemic heart disease (i.e., acute coronary syndrome), and nonischemic heart disease (i.e., valvular heart disease, arrhythmia, cardiomyopathy, and myocarditis).

The Chi-squared test was used to determine differences in the patient characteristics and demographics between the study and comparison groups, as well as differences in the clinical features of patients with new-onset heart failure and those without heart failure. To analyze the association between heart failure and patient age, all patients were classified into three age groups (<60, 60–75, and >65 years). For these three age groups, crude HRs were calculated (for heart failure) using Cox proportional hazards models. Furthermore, to further evaluate the other potential impact factors, the HR was analyzed after adjusting demographics (model 1), medical history (model 2), emergency interventions (model 3), new-onset comorbidities during hospitalization (model 4), and all variables (model 5). The sensitivity analysis was also performed for patients admitted to ICU and those not admitted to ICU (for all OHCA patients and cardiac-caused OHCA patients). All the factors were considered in this analysis, including demographics, emergency interventions, and medical histories (atrial flutter and atrial fibrillation, hypertension, and diabetes mellitus).

Time-related factors associated with the occurrence of new-onset heart failure were also calculated. Heart failure-free survival curves were estimated using the Kaplan–Meier method and log-rank test. Among the patients with heart failure, the time from OHCA to the onset of heart failure was recorded and further divided into three periods (<60, 60–120, and 120–180 days). A p value <0.05 was considered statistically significant.

3. Results

3.1. Characteristics and Demographics of OHCA Patients. During the study period, 49,101 nontraumatic OHCA adult patients survived to ICU admission, 10,185 (20.7%) survived to ICU admission, and 3,767 (7.8%) survived to discharge. The final number of study patients (chosen according to the inclusion and exclusion criteria) was 7,321. The characteristics and medical history of patients in the study ($n = 7,321$) and comparison ($n = 21,963$) groups are presented in Table 1. Compared with patients in the comparison group, those in the study group had a lower economic level. Moreover, the incidence of myocardial infarction, hypertension, diabetes, cardiomyopathy, COPD and asthma, CKD, and liver cirrhosis was significantly higher among OHCA patients (all $p < 0.001$). In addition, 17.1% ($n = 1255$) of OHCA patients had received defibrillation, and 7.3% ($n = 532$) had received catheterization. Only 1.8% and 3.7% of OHCA patients received ECMO and hypothermia therapy, respectively. Nonischemic heart disease and infection were the two most common new-onset comorbidities during hospitalization. The cumulative incidence of heart failure is 3.84%.

3.2. Clinical Features of Patients Who Suffered New-Onset Heart Failure. Among the 7,321 OHCA patients, 363 patients

Table 1: Characteristics of OHCA patients and comparison patients.

Variables	OHCA patients ($n = 7,321$)		Comparison patients ($n = 21,963$)		p value
	No.	%	No.	%	
Sex					
Male	4,528	61.8	13,584	61.8	1.000
Female	2,793	38.2	8,379	38.2	
Age group (y/o)					
<60	2,619	35.8	7,857	35.8	
60–75	1,942	26.5	5,826	26.5	1.000
>75	2,760	37.7	8,280	37.7	
Economic level (monthly income in USD$)*					
<600	2,852	39.0	7,281	33.2	
601–1,000	3,326	45.4	10,330	47.0	<0.001
>1,000	1,143	15.6	4,352	19.8	
Geographic region of Taiwan*					
Northern	3,480	47.5	10,379	47.3	
Central	1,812	24.8	5,045	23.0	<0.001
Southern	1,747	23.9	5,808	26.4	
Eastern	282	3.9	731	3.3	
Urbanization*					
1 (most)	1,722	23.5	5,471	24.9	
2	707	9.7	2,123	9.7	0.052
3	1,812	24.8	5,475	24.9	
4	3,080	42.1	8,894	40.5	
Medical history					
Myocardial infarction*	2,251	30.7	2,251	10.2	<0.001
Hypertension*	3,960	54.1	5,901	26.9	<0.001
Diabetes mellitus*	2,726	37.2	2,498	11.4	<0.001
Cardiomyopathy*	44	0.6	12	0.1	<0.001
COPD[a] and asthma*	2,677	36.6	3,122	14.2	<0.001
CKD[b*]	1,086	14.8	452	2.1	<0.001
SLE[c*]	22	0.3	19	0.1	<0.001
Liver cirrhosis*	442	6.0	243	1.1	<0.001
Sicca syndrome*	111	1.5	178	0.8	<0.001
Rheumatic arthritis*	119	1.6	166	0.8	<0.001
Emergency intervention for OHCA					
Defibrillation*	1,255	17.1	4	0.02	<0.001
PCI[d*]	532	7.3	29	0.1	<0.001
ECMO[e*]	135	1.8	—[f]	—[f]	<0.001
Therapeutic hypothermia*	268	3.7	3	0.01	<0.001
New-onset comorbidity during hospitalization					
Infection*	1,909	26.1	306	1.4	<0.001
Heart disease					
Ischemic*	685	9.4	33	0.2	<0.001
Nonischemic*	3,975	54.3	23	0.1	<0.001

[a]COPD: chronic obstructive pulmonary disease; [b]CKD: chronic kidney disease; [c]SLE: systemic lupus erythematosus; [d]PCI: percutaneous coronary intervention; [e]ECMO: extracorporeal membrane oxygenation. *Statistically significant difference. [f]Data were not allowed to be displayed if extraction with certain specific parameters resulted in an output of less than 3 patients (identification possible).

(4.9%) suffered new-onset heart failure during the follow-up period. Their clinical features compared with those of the patients without heart failure are shown in Table 2. Patients older than 75 years accounted for the majority of patients with heart failure. Myocardial infarction, hypertension, and cardiomyopathy were significantly more common in heart failure patients (all $p < 0.05$). Additionally, significantly more patients with and without heart failure received defibrillation and PCI in the ED (both $p < 0.05$).

3.3. HRs for New-Onset Heart Failure in Different Age Groups. The covariate-adjusted HRs for new-onset heart failure were significantly higher in OHCA patients than in comparison patients (Table 3). Moreover, we found that a variety of HRs differed among the age groups. OHCA patients who are 60–75 years old had a higher covariate-adjusted HR (HR: 11.4, 95% CI: 9.0–14.4) than those who are <60 years old (HR: 5.6, 95% CI: 4.3–7.3) and >75 years old (HR: 10.7, 95% CI: 8.5–13.4). In addition, the risk of heart failure was much

Table 2: Clinical features of patients who suffered new-onset heart failure.

	Total OHCA patients ($n = 7,321$)		p value
	New-onset heart failure		
	Yes ($n = 363$) No. (%)	No ($n = 6,958$) No. (%)	
Male	210 (57.9)	4,318 (62.1)	0.108
Age group (y/o)*			
<60	96 (26.4)	2523 (36.3)	
61–75	122 (33.6)	1820 (26.2)	<0.001
>75	145 (39.9)	2615 (37.6)	
Medical history			
Myocardial infarction*	183 (50.4)	2,068 (29.7)	<0.001
Hypertension*	230 (63.4)	3,730 (53.6)	<0.001
Diabetes mellitus	149 (41.0)	2,577 (37.0)	0.133
Cardiomyopathy*	10 (2.8)	34 (0.5)	<0.001
COPD and asthma	142 (39.1)	2,535 (36.4)	0.314
CKD	64 (17.6)	1,022 (14.7)	0.130
Emergency intervention			
Defibrillation*	79 (21.8)	1,176 (16.9)	0.018
PCI*	105 (28.9)	427 (6.1)	<0.001
ECMO	5 (1.4)	130 (1.9)	0.687
Therapeutic hypothermia	17 (4.7)	251 (3.6)	0.313
New-onset comorbidity during hospitalization			
Infection*	118 (32.5)	1,791 (25.7)	0.006
Heart disease			
Ischemic*	92 (25.3)	593 (8.5)	<0.001
Nonischemic*	160 (44.1)	3,815 (54.8)	<0.001

*Statistically significant difference.

Table 3: Covariate-adjusted HRs for new-onset heart failure in different age groups during the 6-month follow-up period.

New-onset heart failure	Total ($n = 29,284$)		OHCA patients ($n = 7,321$)		Comparison patients ($n = 21,963$)	
	No.	%	No.	%	No.	%
All patients	553	1.9	281	3.8	272	1.2
Crude HR[a] (95% CI[b])	—		8.8* (7.45–10.5)	1.00		
Age <60 years	—		73	2.8		
Crude HR[a] (95% CI[b])	—		5.6* (4.3–7.3)			
Age 60–75 years	—		95	4.9		
Crude HR[a] (95% CI[b])	—		11.4* (9.0–14.4)			
Age >75 years	—		113	4.1		
Crude HR[a] (95% CI[b])	—		10.7* (8.5–13.4)			

[a]HR: hazard ratio; [b]CI: confidence interval; * $p < 0.05$.

higher in cardiac-caused OHCA groups ($n = 3,040$, 41.5%). Among them, the crude HRs were significantly higher than comparison patients (Supplementary Material 1).

3.4. Variables Influencing the Risk of New-Onset Heart Failure. The adjustments for likely influencing factors are presented in Table 4. The risks of heart failure were more predominant in the sensitivity analysis conducted on emergency interventions and medical histories (hypertension, atrial flutter/atrial fibrillation, and diabetes mellitus) (data not shown).

3.4.1. Medical History. For all OHCA patients, myocardial infarction, hypertension, cardiomyopathy, and flutter/atrial fibrillation were strongly associated with the occurrence of heart failure. Myocardial infarction and cardiomyopathy had a significant impact in all age groups. Hypertension increased the risk more in those aged >75 years. Moreover, cardiomyopathy was the most powerful risk factor in those aged <60 years (HR: 4.62, 95% CI: 1.89–11.29).

3.4.2. Emergency Interventions. In all age groups, patients who had ever required emergency PCI or defibrillation were at a higher risk of heart failure (model 3). While ECMO decreased the risk of heart failure (HR: 0.23, 95% CI: 0.07–0.73), therapeutic hypothermia did not.

Table 4: Variables influencing the risk of new-onset heart failure according to different age groups.

Models and variables	All patients HR (95% CI)	Adjusted HRs for new-onset heart failure <60 years HR (95% CI)	60–75 years HR (95% CI)	>75 years HR (95% CI)
Model 1	8.68 (7.33–10.29)[b]	5.48 (4.22–7.12)[b]	11.20 (8.83–14.20)[b]	10.49 (8.38–13.15)[b]
Comparison patients[a]	1.00	1.00	1.00	1.00
Model 2	5.21 (4.30–6.30)[b]	4.15 (3.16–5.43)[b]	5.36 (4.08–7.04)[b]	4.83 (3.71–6.30)[b]
Comparison patients[a]	1.00	1.00	1.00	1.00
Myocardial infarction	2.47 (2.05–2.98)[b]	2.86 (2.25–3.65)[b]	2.84 (2.24–3.59)[b]	2.38 (1.88–2.99)[b]
Hypertension	1.67 (1.38–2.02)[b]	1.75 (1.38–2.22)[b]	1.61(1.28–2.04)[b]	1.80 (1.43–2.27)[b]
Cardiomyopathy	2.94 (1.45–5.94)[b]	4.62 (1.89–11.29)[b]	1.21 (0.30–4.90)	3.50 (1.11–11.03)[b]
Diabetes mellitus	1.03 (0.84–1.26)	1.02 (0.77–1.35)	1.02 (0.78–1.32)	1.00 (0.78–1.29)
COPD and asthma	1.35 (1.12–1.62)[b]	1.84 (1.46–2.33)[b]	1.68 (1.34–2.11)[b]	1.47 (1.17–1.85)[b]
CKD	1.25 (0.95–1.65)	1.40 (0.91–2.15)	1.24 (0.85–1.82)	1.49 (1.05–2.11)[b]
Liver cirrhosis	0.86 (0.48–1.53)	0.58 (0.24–1.40)	0.74 (0.30–1.78)	1.36 (0.67–2.74)
Atrial flutter/atrial fibrillation	2.02 (1.47–2.78)[b]	3.78 (2.47–5.76)[b]	2.37 (1.56–3.58)[b]	2.40 (1.66–3.47)[b]
Model 3	6.47 (5.34–7.84)[b]	3.13 (2.19–4.74)[b]	7.04 (5.22–9.51)[b]	8.84 (6.91–11.31)[b]
Comparison patients[a]	1.00	1.00	1.00	1.00
Defibrillation	1.36 (1.01–1.83)[b]	1.42 (0.84–2.40)	2.21 (1.41–3.47)[b]	1.03 (0.56–1.87)
PCI	3.95 (3.01–5.18)[b]	5.58 (3.44–9.05)[b]	3.73 (2.41–5.77)[b]	5.78 (3.69–9.03)[b]
ECMO	0.23 (0.07–0.73)[b]	0.40 (0.12–1.29)	—[c]	—[c]
Therapeutic hypothermia	0.87 (0.50–1.53)	1.01 (0.44–2.33)	1.05 (0.46–2.43)	0.56 (0.08–4.03)
Model 4	5.45 (4.27–6.97)[b]	1.57 (0.98–2.50)	4.36 (2.88–6.60)[b]	5.40 (3.74–7.79)[b]
Comparison patients[a]	1.00	1.00	1.00	1.00
Infection	1.53 (1.20–1.94)[b]	3.15 (2.17–4.57)[b]	2.60 (1.80–3.74)[b]	2.34 (1.66–3.31)[b]
Ischemic heart disease	4.50 (3.46–5.86)[b]	6.72 (4.34–10.42)[b]	5.74 (3.80–8.65)[b]	6.39 (4.14–9.85)[b]
Nonischemic heart disease	1.12 (0.88–1.42)	2.16 (1.33–3.51)[b]	1.46 (0.97–2.20)	0.99 (0.68–1.46)
Model 5	3.20 (2.44–4.19)[b]	1.25 (0.77–2.05)	1.92 (1.23–3.00)[b]	2.66 (1.81–3.92)[b]
Comparison patients[a]	1.00	1.00	1.00	1.00

[a]Reference group; [b]$p < 0.05$; [c]data were not allowed to be displayed if extraction with certain specific parameters resulted in an output of less than 3 patients (identification possible); Model 1: adjusted by demographics. Model 2: adjusted by medical history. Model 3: adjusted by emergency interventions. Model 4: adjusted by new-onset comorbidities during hospitalization. Model 5: adjusted by all variables (models 1–4).

3.4.3. New-Onset Comorbidities during Hospitalization. New-onset ischemic heart disease occurring during hospitalization was the comorbidity with the most influence on the occurrence of heart failure (model 4). Furthermore, we found that ischemic heart disease strongly increased the risk of heart failure in patients aged <60 years (HR: 6.72, 95% CI: 4.34–10.42).

3.5. Heart Failure-Free Survival. The heart failure-free survival curves of the study and comparison patients during the follow-up period are shown in Figure 2. The incidence of heart failure-free survival was significantly lower in OHCA patients than in comparison patients (all age groups, $p < 0.05$). Heart failure occurred more quickly in patients aged 61–75 years (Figure 2(c)) than in those in the other age groups (Figures 2(a), 2(b), and 2(d)).

3.6. Time between OHCA and Heart Failure Onset. The time between OHCA and new-onset heart failure is shown in Figure 3. For all age groups, most (58.2%) heart failure events occurred within 60 days after OHCA, especially in patients younger than 60 years (<60 years: 72%, 60–75 years: 63.5%, and >70 years: 52.7%). In addition, a delayed onset (121–180 days) of heart failure was more common in those aged >75 years (19.2%) than in those aged <60 years (11%) and 61–75 years (15.3%).

4. Discussion

Myocardial dysfunction has been reported as a common comorbidity during the early postresuscitation period, occurring in up to 66% of ROSC patients [10]. This presentation would peak between 2 and 5 hours after CPR [6–9,11]. Myocardial dysfunction is usually induced by ischemia/reperfusion (I/R) injury, systemic inflammatory responses, and catecholamine surges [9]. Damage to the myocardium can cause low cardiac output, unstable hemodynamics, and even neurological impairment [9]. Despite this condition being critical, some studies have reported that it is a short-term comorbidity and could be reversible within 72 hours [9–11].

We found that the risk of new-onset heart failure was higher in long-term OHCA survivors than in comparison patients. The first key risk factor was age. Some previous studies have reported that the risk of heart failure increased in proportion with patient age [21, 22]. However, in this study, compared with the younger and older patients, patients aged 60 to 75 years showed the highest risk. One reason might be that cardiovascular disease (e.g., coronary artery disease) was more common in this age group [23–25]. However,

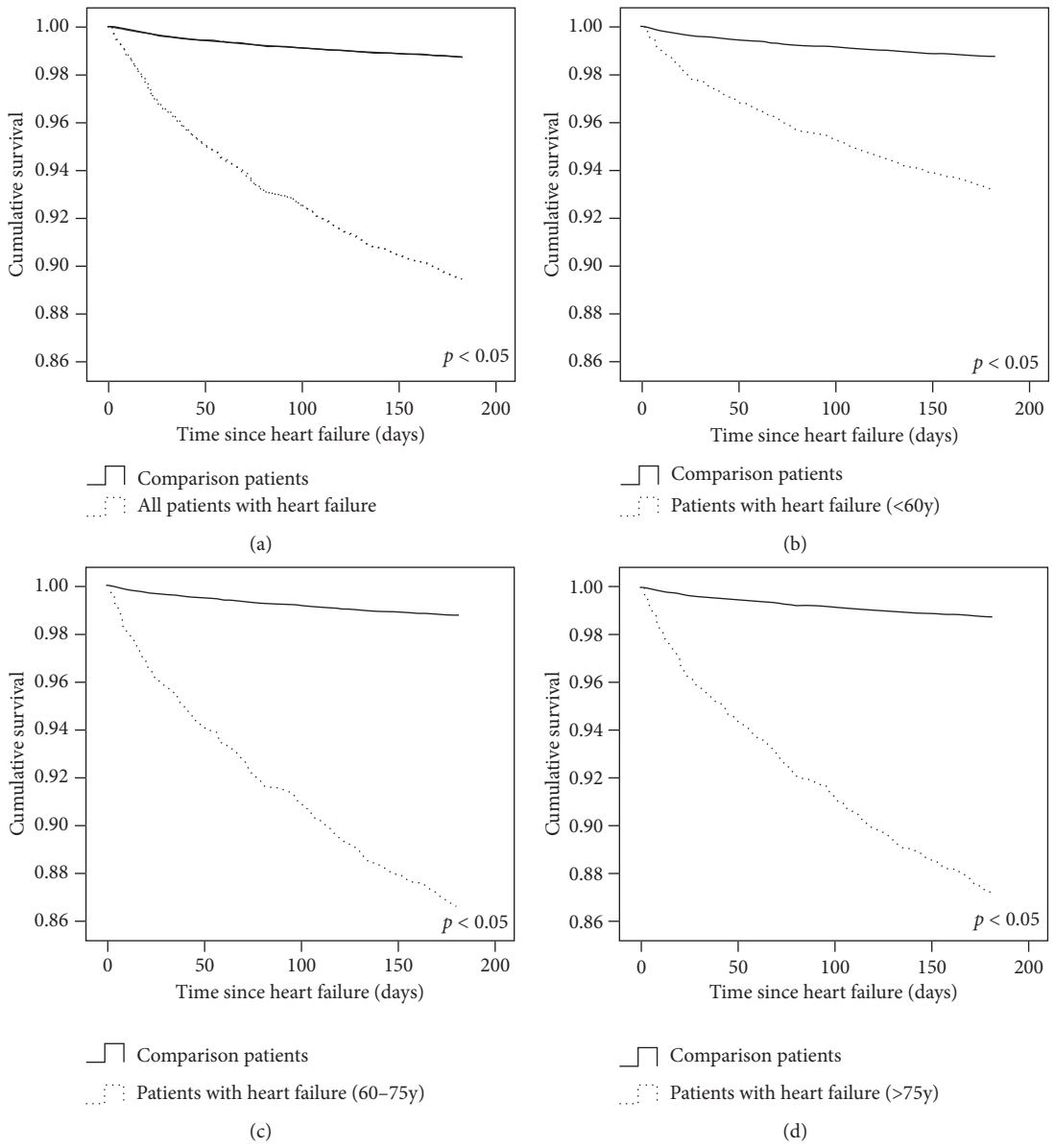

Figure 2: The heart failure-free survival curves of study and comparison patients during the follow-up period. The incidence of heart failure-free survival was significantly lower in OHCA patients than comparison patients (all age groups, $p < 0.05$). Heart failure occurred more quickly in patients aged 61–75 years (Figure 2(c)) than in those in the other age groups (Figures 2(a), 2(b), and 2(d)).

heart failure normally increased with age, and our findings also need to consider potential survival bias.

The second key risk factor for new-onset heart failure was a history of myocardial infarction, hypertension, or cardiomyopathy. Our analysis showed that a history of diabetes mellitus, COPD/asthma, and CKD did not significantly increase the risk. Myocardial infarction and cardiomyopathy were the most powerful risk factors, increasing the risk in all age groups. We suspect that myocardial damage would be worse in OHCA patients with a history of myocardial infarction or a certain extent of myocardial stunning, which might result in poorer coronary perfusion during resuscitation or the postresuscitation period. This condition might further cause irreversible myocardial dysfunction and long-term heart failure [6, 7]. A history of cardiomyopathy was a risk factor only in patients aged less than 60 years. The major reason for this finding is that young patients with earlier gene presentation (e.g., sarcomere protein mutations) would have more severe mitral valve regurgitation and pulmonary artery wedge pressure [26–29]. We suspect that pulmonary hypertension and left ventricle outlet obstruction could be more predominant after resuscitation and thus increase the risk of heart failure. In addition, the heart failure itself includes several types of cardiomyopathies. However, we suspect that cardiomyopathy would be a strong risk factor and even be a confounding factor. Therefore, we did not exclude those patients and try to put them in our regression models.

The occurrence of new-onset comorbidities during hospitalization was the third key risk factor for heart failure;

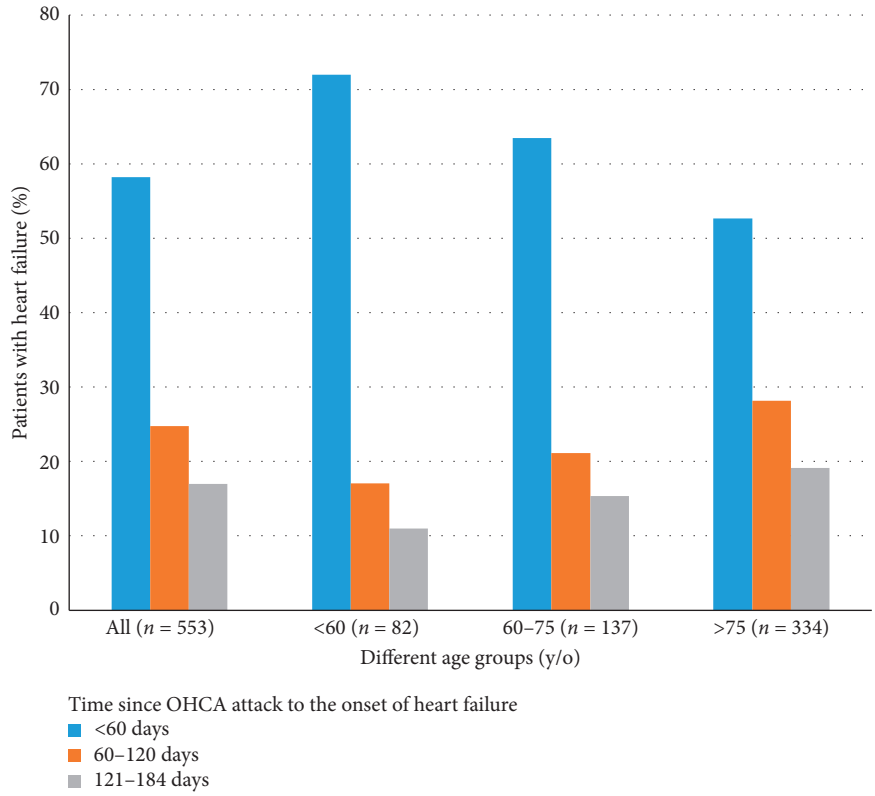

Figure 3: The time between OHCA and new-onset heart failure.

ischemic heart disease occurring during hospitalization significantly increased this risk. As the cardiac output, rhythms, vascular resistance, and contraction ability are unstable during the postresuscitation period, [6–8,10] new-onset diseases affecting the heart could independently increase the cardiovascular load and result in irreversible heart failure. Therefore, aggressive heart disease prophylaxis and treatment during the early postresuscitation period should be emphasized. In addition, in our adjusted models, infection increased the risk of new-onset heart failure in the long-term follow-up period. Some previous studies have also demonstrated that severe infection could increase OHCA-related mortality and impair hemodynamics during ICU admission [9, 30].

The final key factors were emergency interventions, and we found that emergency defibrillation and PCI both increased the risk of heart failure. The two interventions would be performed for acute coronary syndrome and shockable rhythms. In addition, the two interventions can directly achieve reperfusion of the coronary artery and control life-threatening arrhythmias, which is beneficial for restricting the infarction area and stabilizing the hemodynamics. However, patients presenting with cardiac arrest might have severe myocardial damage that is not completely reversible, thus reducing the efficacy of emergent PCI and defibrillation. In addition, although some studies have demonstrated that hypothermia might benefit patients by decreasing infarction area resulting from ST-elevation myocardial infarction (STEMI) in the early post-PCI period (i.e., the first 3 days) [31–33], in this study, only ECMO significantly decreased the risk of heart failure. We suspect the major reason was that ECMO would provide higher chance (or more time) to handle cardiac diseases (i.e., ACS or acute myocarditis) [34, 35]. Once the cardiac diseases were well treated, ECMO could be thought to reduce the risk of following cardiac complications (including heart failure) [36]. Further large randomized controlled trials should be conducted to demonstrate this therapeutic effect of decreasing the risk of new-onset heart failure in OHCA patients. Time-related factors were also considered in this study. We found that most heart failure events occurred within 60 days after OHCA, especially in patients less than 60 years of age. Therefore, early heart function evaluation and treatment should be considered routine for OHCA patients. Finally, prehospital information did not include in this database. Although the associations between prehospital interventions and postresuscitation heart functions had not been clearly addressed, some previous studies pointed out that bystander CPR, public defibrillation were strong predictors of survival (even good neurologic outcome) [37, 38]. Therefore, we reasonably suspect those prehospital interventions would more likely associate with preserved heart functions.

In conclusion, an age from 61–75 years, a history of myocardial infarction or cardiomyopathy, and ischemic heart disease or infection occurring as comorbidities during hospitalization were strong risk factors for new-onset heart failure in OHCA patients. However, ECMO significantly decreased this risk. More importantly, most heart failure events occurred within 60 days after OHCA.

4.1. Limitations. We meticulously selected our target patients using specific ICD-9 codes. However, relevant information mentioned in previous studies regarding causes of myocardial dysfunction could not be accessed because this study was based on data from the LHID. Moreover, based on government regulations, the data of patients in small groups based on certain criteria were hidden and could not be analyzed. These are inherent limitations to using the LHID database. However, this is the first study to reveal different degrees of risk for post-OHCA heart failure in different patient age groups. These findings indicate a new direction for studying heart failure after cardiac arrest and possible root causes that need to be clarified. In fact, this database was designed for making national health policy. Therefore, it only included demographics, diagnosis, costs, treatments, and final outcomes. Some detailed medical information (i.e., prehospital factors, findings of echocardiography, and data of recovery) were not available in this database. We hope this article could initially induce the interest of readers in this new topic. Some nature limitations of this study could be handled in our next research project (multicenter studies).

Data Availability

This is a national database study. With the government's permission (need proposal), data from the database could be extracted and analyzed for the purpose of scientific research.

Conflicts of Interest

There are no conflicts of interest related to this study.

Authors' Contributions

Cheng Hsu Chen and Chih-Yu Chang contributed equally to this work.

Supplementary Materials

Covariate-adjusted HRs for new-onset heart failure in cardiac-caused OHCA patients. (*Supplementary Materials*)

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Research Article

Comparison of Injury Severity Score, Glasgow Coma Scale, and Revised Trauma Score in Predicting the Mortality and Prolonged ICU Stay of Traumatic Young Children: A Cross-Sectional Retrospective Study

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Introduction. The purpose of this study was to examine the capacity of commonly used trauma scoring systems such as the Glasgow Coma Scale (GCS), Injury Severity Score (ISS), and Revised Trauma Score (RTS) to predict outcomes in young children with traumatic injuries. *Methods*. This retrospective study was conducted for the period from 2009 to 2016 in Kaohsiung Chang Gung Memorial Medical Hospital, a level I trauma center. We included all children under the age of 6 years admitted to the hospital via the emergency department with any traumatic injury and compared the trauma scores of GCS, ISS, and RTS on patients' outcome. The primary outcomes were mortality and prolonged Intensive Care Unit (ICU) stay, with the latter defined as an ICU stay longer than 14 days. The secondary outcome was the hospital length of stay (HLOS). Receiver operating characteristic (ROC) analysis was also adopted with the value of the area under the ROC curve (AUC) for comparing trauma score prediction with patient mortality. Cutoff values from each trauma score for mortality prediction were also measured by determining the point along the ROC curve where Youden's index was maximum. *Results*. We included a total of 938 patients in this study, with a mean age of 3.1 ± 1.82 years. The mortality rate was 0.9%, and 93 (9.9%) patients had a prolonged ICU stay. An elevated ISS (34 ± 19.9 vs. 5 ± 5.1, $p = 0.004$), lower GCS (8 ± 5.0 vs. 15 ± 1.3, $p = 0.006$), and lower RTS (5.58 ± 1.498 vs. 7.64 ± 0.640, $p = 0.006$) were all associated with mortality. All three scores were considered to be independent risk factors of mortality and prolonged ICU stay and had a linear correlation with increased HLOS. With regard to predicting mortality, ISS has the highest AUC value (ISS: 0.975; GCS: 0.864; and RTS: 0.899). The prediction cutoff values of ISS, GCS, and RTS on mortality were 15, 11, and 7, respectively. *Conclusion*. Regarding traumatic injuries in young children, worse ISS, GCS, and RTS were all associated with increased mortality, prolonged ICU stay, and longer hospital LOS. Of these scoring systems, ISS was the best at predicting mortality.

1. Introduction

Trauma is considered a big threat to childhood survival. The National Center for Health Statistics in the United States has indicated that unintentional injury is the leading cause of death and disability in children [1]. Managing pediatric trauma events at the emergency department (ED) is often a challenge because children have less fat and more elastic connective tissue covering a flexible skeleton that protects packed abdominal and thoracic structures [2]. As a result, the impact and causes of trauma can vary considerably among different age groups. The anatomical, physiological, and emotional differences between adults and children imply that children are not just adults on a smaller scale [3].

In the past, most studies related to trauma assessment have investigated pediatric patients with ages ranging from about 0–18 years [4, 5]. Nevertheless, age-based studies focused on younger victims have not been common. Managing traumatic injury in young children is different from adults as children's compensatory responses to large numbers of blood loss, hypoxia, severe trauma, and burns differ significantly [6]. Furthermore, young patients often do not have enough vocabulary, resulting in limited expression, especially for children under two years of age [7, 8]. Young children also have difficulty in accurately expressing their feelings when a medical history is taken and are often irritated and crying upon arriving at the hospital due to pain or fright. Therefore, trauma scores related to vital signs and physical examinations are more objective and accessible [9]. Obtaining trauma scores earlier allows critical intervention. In this study, we aimed to investigate several commonly used traumatic scores on the outcomes of young children, including mortality, prolonged ICU stay, and hospital length of stay (HLOS).

2. Materials and Methods

2.1. Trauma Scores Selection. Various quantitative scoring systems have been proposed to evaluate trauma severity and outcome, but most of them were not age specific, and each had its own limitations [10–13]. Considering the different physiological structures in younger children, we selected the Injury Severity Score (ISS), which emphasizes anatomic criteria and has been validated to predict prognosis [14]. In previous studies, major trauma in the pediatric category has been defined as an Injury Severity Score greater than 15 [15, 16]. However, few studies have focused on ISS performance in young children [17]. Despite a number of proposed modifications and alternate scoring systems, ISS remains the most widely used to define severely injured patients, which is why we chose it [16, 18, 19].

The Glasgow Coma Scale (GCS) indicates level of consciousness and has always been evaluated upon patient arrival. This scale has been frequently used for decades as blunt head trauma is a common cause of mortality and morbidity in pediatric injuries [20–23]. Since head injury is one of the most common traumatic mechanisms in young children, GCS is also appropriate for our study's main group.

The Revised Trauma Score (RTS) is used in prehospital practices worldwide, can be obtained immediately, and includes the GCS, systolic blood pressure, and respiratory rate. The formula for calculating RTS is as follows: RTS = 0.7326 ∗ systolic blood pressure + 0.2908 ∗ respiratory rate + 0.9368 ∗ GCS [24].

2.2. Study Population and Design. This retrospective study was conducted from January 1, 2009, to December 31, 2016, in Kaohsiung Chang Gung Memorial Medical Hospital, a level I trauma center in southern Taiwan. The Institutional Review Board of the Chang Gung Medical Foundation approved the medical information, and all patients' and physicians' records and information were anonymized and deidentified prior to analysis (IRB number: 201801721B0). Additional detailed information of all trauma patients was retrieved from the studied institution's trauma registry system, including age, gender, initial vital signs, cause of injury, different types of trauma severity scores, hospital length of stay (LOS), intensive care unit (ICU) stay, and mortality.

This study consisted of children under the age of 6 years with any type of traumatic injury who were admitted to the hospital via the ED. Patients with a pre-existing medical condition that contributed to the trauma incident and who died in the ED were excluded. We used vital signs and GCSs at triage for scoring, comparing the accuracy of the GCS, ISS, and RTS trauma scores on predicting patients' outcome. Initial triage and vital signs were obtained by senior and well-trained emergency nurses, and child-version sphygmomanometer was used for young children. ISS was measured by the trauma physicians in charge in the ED.

The primary outcomes were trauma-related mortality during admission and prolonged ICU stay, which was defined as an ICU stay longer than 14 days. Prolonged ICU stay is usually defined as ≥14 days admission in the ICU, which has been considered with resource utilization and patients' morbidity and mortality [25–29]. The HLOS was considered as the secondary outcome in patients who survived beyond admission. Patients who expired before admission were excluded from prolonged ICU stay and HLOS analysis.

2.3. Statistical Analysis. Trauma scores' contribution to outcomes including mortality and prolonged ICU stay was analyzed by Student's *t*-test and validated using binary regression after adjusting for age, gender, and cause of injury. Linear regression was used to observe the correlation between trauma scores and HLOS.

We further drew the receiver operating characteristic (ROC) curve and calculated the value of the area under the ROC curve (AUC) to compare trauma scores prediction with patient mortality. Cutoff values from each trauma score for mortality prediction were also measured by determining the point along the ROC curve where Youden's index was maximum [30]. The capability of trauma scores in predicting the mortality and prolonged ICU stay was calculated using the Chi-squared test. All statistical analysis was conducted with SPSS (version 22).

3. Results

This study consisted of a total of 938 patients, with a mean age of 3.1 ± 1.82 years. The overall mortality rate was 0.9%. The rate of ICU stay was 41.7% (N = 391), with a mean ICU stay of 10.2 ± 7.83 days. Regarding the cause of trauma, injury from fall, traffic accident, and burn injury accounted for 86.7% of all admitting injuries. The average trauma scores of ISS, GCS, and RTS in the general population were 4.9 ± 6.0, 14.7 ± 1.4, and 7.62 ± 0.68, respectively (Table 1). We excluded 25 patients from RTS and outcome analysis since their initial blood pressure had not been obtained.

Table 2 shows the trauma scores between patients of both the mortality and survival groups compared with student's t-test. The ISS score was statistically higher in the mortality group (34 ± 19.9 vs. 5 ± 5.1, $p = 0.004$), while GCS (8 ± 5.0 vs. 15 ± 1.3, $p = 0.006$) and RTS (5.58 ± 1.498 vs. 7.64 ± 0.640, $p = 0.006$) scores were lower. When comparing different trauma scores with prolonged ICU stay, only RTS demonstrated a significant difference between the two studied groups (7.34 ± 1.019 vs. 7.67 ± 0.577; $p = 0.004$) (Table 2).

As shown in Table 3, the logistic regression regarding trauma scores' in association with primary and secondary outcomes is displayed. ISS (aOR: 1.17, 95% CI: 1.091–1.225), GCS (aOR: 0.59, 95% CI: 0.492–0.714), and RTS (aOR: 0.19, 95% CI: 0.094–0.373) were all considered to be independent risk factors of mortality and prolonged ICU stay. In addition, younger age and burn injury were also risk factors for prolonged ICU stay. All three trauma scores' changes had a positive effect on HLOS, and these effects were found to be statistically significant (Table 3).

Figure 1 shows the ROC curves of different trauma scores related to outcomes. Upon calculating the AUC value (Table 4), all trauma scores revealed acceptable prediction ability for mortality (ISS: 0.975, 95% CI: 0.940~1; GCS: 0.864, 95% CI: 0.682~1; RTS: 0.899, 95% CI: 0.759~1) but not for prolonged ICU stay (ISS: 0.502, 95% CI: 0.384~0.513; GCS: 0.426, 95% CI: 0.447~0.572; RTS: 0.578, 95% CI: 0.520~0.653). We further measured the cutoff value for mortality prediction of each trauma score according to the ROC curves, which were found to be 15 for ISS, 11 for GCS, and 7 for RTS.

The evaluation of each trauma score's cutoff value regarding mortality is provided in Table 5. Using ISS ≥ 15 as the cutoff value for predicting mortality, its positive predictive value (PPV) was 11.1%, while its negative predictive value (NPV) was 99.9% ($p < 0.001$, OR = 109.25). Meanwhile, GCS ≤ 11 had a PPV of 23.1% and NPV of 99.8% for predicting mortality ($p < 0.001$, OR = 136.50). Finally, using RTS ≤ 7 as a predictor for mortality resulted with a PPV of 9.9% and NPV of 99.9% ($p < 0.001$, OR = 94.72).

Table 1: Epidemiology of trauma patients under the age of six years admitted via the pediatric emergency department.

	Variables	Number (%)/mean ± SD
	Total	938 (100%)
	Age (years)	3.1 ± 1.82
	BMI	16.6 ± 4.40
Gender	Male	554 (59.1%)
	Injury from fall	329 (35.1%)
	Traffic accident	134 (14.3%)
Cause of injury	Burn injury	351 (37.4%)
	Blunt/crushing injury	71 (7.6%)
	Other	53 (5.7%)
	Mortality	8 (0.9%)
	ICU admission	391 (41.7%)
Outcome	Prolonged ICU stay	93 (9.9%)
	Length of ICU stay (days)	10.2 ± 7.83
	Length of hospital stay (days)	6.9 ± 7.69
	ISS	4.9 ± 6.0
Trauma score	GCS	14.7 ± 1.4
	RTS	7.62 ± 0.68

BMI = body mass index; ICU = intensive care unit; ISS = Injury Severity Score; GCS = Glasgow Coma Scale; RTS = Revised Trauma Score.

4. Discussion

In this study, we included all patients admitted to the trauma center younger than the age of 6 years, with a mean age of 3.1 years and an overall mortality rate of 0.9%. As in previous studies, the mortality rate of pediatric trauma was approximately 2% [31, 32]. The three most common causes of trauma in this study were, in order, injury from fall, traffic accident, and burn injury. Adegoke et al. reported similar findings, while Derakhshanfar et al. reported traffic accidents to be the most common cause, followed by fall injuries [33–35].

The trauma score systems selected in this study were ISS, GCS, and RTS since their values were easy to obtain and calculate. Furthermore, consciousness level is the main domain of these trauma scores since brain injury is the primary cause of mortality and morbidity in pediatric injuries [36]. The average trauma scores of ISS, GCS, and RTS in our studied population were 4.9, 14.7, and 7.62, respectively. In contrast, the average trauma scores were 34, 8, and 5.58 among patients who died. In previous studies, these trauma scores in survivor and mortality populations have traditionally varied. Yousefzadeh Chabok et al. demonstrated an ISS of 6.5 overall and 17.7 in the mortality group, with GCS scores of 4.7 in the mortality group and 14.6 in the survivor group [32]. Soni et al. showed RTS scores of 7.13 in trauma survivors and 4.39 in nonsurvivors, with ISS scores of 11.68 in the mortality group and 11.87 in the survivor group [37]. In our study, all trauma scores differed with statistical significance between the survivor and mortality groups.

After adjusting for gender, age, and traumatic mechanism using binary regression, lower GCS and RTS levels still appeared to be associated with increased mortality and prolonged ICU stay. Increased ISS scores also have a positive effect on higher mortality and prolonged ICU stay rates, though the latter did not demonstrate statistical difference.

As for secondary outcomes, all three trauma scores demonstrated a linear correlation with hospital length of stay after adjusting for age, gender, and trauma mechanism

Table 2: Comparison of trauma scores in different groups of mortality and prolonged ICU stay.

Trauma score	Mortality	Survival	p-value	ICU stay ≥ 14 days	ICU stay < 14 days	p-value
	Mean ± SD			Mean ± SD		
ISS	34 ± 19.9	5 ± 5.1	**0.004**	4 ± 5.0	5 ± 5.1	0.237
GCS	8 ± 5.0	15 ± 1.3	**0.006**	15 ± 1.8	15 ± 1.2	0.415
RTS	5.58 ± 1.498	7.64 ± 0.640	**0.006**	7.34 ± 1.019	7.67 ± 0.577	**0.004**

SD = standard deviation; ISS = Injury Severity Score; GCS = Glasgow Coma Scale; RTS = Revised Trauma Score.

Table 3: Logistic regression for trauma score to mortality, prolonged ICU stay, and hospital length of stay (after adjusting for age, gender, and cause of injury).

Variables	aOR	95% CI	aOR	95% CI	β coefficient	95% CI
	Mortality		*Prolonged ICU stay*		*Hospital length of stay*	
Age	0.983	0.609–1.625	0.809*	0.707–0.925	−0.602*	−0.849~−0.355
Male	3.293	0.353–30.594	1.021	0.651–1.602	−0.426	−1.311~0.459
Injury from fall	1.239	0.188–8.148	0.079*	0.029–0.218	−6.099*	−7.016~−5.183
Traffic accident	3.393	0.453–25.155	0.122*	0.029–0.516	−1.511*	−2.911~−0.111
Burn injury	0.092	0.001–14.410	18.199*	8.931–37.085	8.609*	7.701~9.516
Blunt/crushing injury	—	—	0.526	0.186–1.491	−1.317	−3.049~0.414
Others	—	—	0.532	0.161–1.752	−1.032	−3.015~0.952
ISS	**1.17**	**1.091–1.225**	**1.034**	**1.004–1.063**	**0.315**	**0.224~0.401**
Age	1.164	0.726–1.865	0.818	0.715–0.936	−0.536*	−0.792~−0.280
Male	1.053	0.194–5.727	0.99	0.631–1.552	−0.437	−1.353~0.479
Injury from fall	0.550	0.084–3.614	0.081*	0.029–0.225	−5.497*	−6.434~−4.559
Traffic accident	3.788	0.719–19.949	0.005*	0.029–0.525	−0.505	−1.890~0.879
Burn injury	1.062	0.142–7.939	15.92*	8.046–31.500	7.198*	6.625~8.130
Blunt/crushing injury	0	—	0.497	0.174–1.420	−1.682	−3.438~0.074
Others	0	—	0.526	0.160–1.733	−1.441	−3.451~0.569
GCS	**0.59**	**0.492–0.714**	**0.82**	**0.692–0.970**	**−0.783**	**−1.174~−0.393**
Age	1.334	0.857–2.076	0.853	0.744–0.977	−0.406	−0.663~−0.149
Male	1.134	0.225–5.719	1.041	0.661–1.639	−0.317	−1.222~0.589
Injury from fall	1.159	0.194–6.922	0.085*	0.031–0.234	−5.287	−6.217~4.356
Traffic accident	8.822*	1.662–46.835	0.131*	0.031–0.547	−0.357	−1.713~0.999
Burn injury	0.143	0.019–1.078	12.591*	6.675–23.749	6.703	5.775~7.631
Blunt/crushing injury	0	—	0.531	0.186–1.518	−1.463	−3.196~0.270
Others	0	—	0.548	0.166–1.812	−1.311	−3.294~−0.673
RTS	**0.19**	**0.094–0.373**	**0.69**	**0.534–0.896**	**−2.981**	**−4.209~−1.752**

(Table 4). This result was similar to a previous study in China that showed that increased ISS and decreased RTS were correlated with an increased length of hospital stay [38].

Regarding mortality prediction, ROC curve analysis indicated that all three scoring systems were statistically significant (Table 4). While some previous studies demonstrated that GCS can better predict mortality [32, 39], in our study, although the difference was small, we showed ISS to be the strongest predictor of mortality. However, none of the three trauma scoring systems could predict prolonged ICU stays with significance.

The cutoff values selected from the ROC analysis of ISS, GCS, and RTS were 15, 11, and 7, respectively. A similar cutoff value for ISS was reported in a previous study by Yousefzadeh Chabok et al. [38]. Both the sensitivity and specificity for mortality prediction regarding the selected cutoff values from each trauma score system were high (Table 5). However, all the selected cutoff values had much higher NPV than PPV on mortality prediction, which suggests that the cutoff values of all three trauma score systems were better at predicting survival than mortality.

5. Limitations

This study has certain limitations. This retrospective study was conducted in a single medical center, which may limit the generalizability of the conclusions. All possible confounding factors were unmodifiable, and a cause-and-effect relationship could not be determined. The assessment of trauma scores was performed by different trained medical personnel throughout the study period, which may have led to interpersonal bias.

Furthermore, the overall mortality rate of our study was 0.9% among the 938 patients, which was less than our reference in previous literature, and the accuracy in using trauma scoring systems may differ. Moreover, since the most traumatic mechanism in our study was burn injuries, an ISS may be falsely elevated when a patient has minor burns on various body parts. In contrast, the severity of burn injuries may be underestimated by trauma scoring systems in a patient with severe, widespread cutaneous burns.

Despite these limitations, the results from this study can help distinguish low-risk patients for mortality and

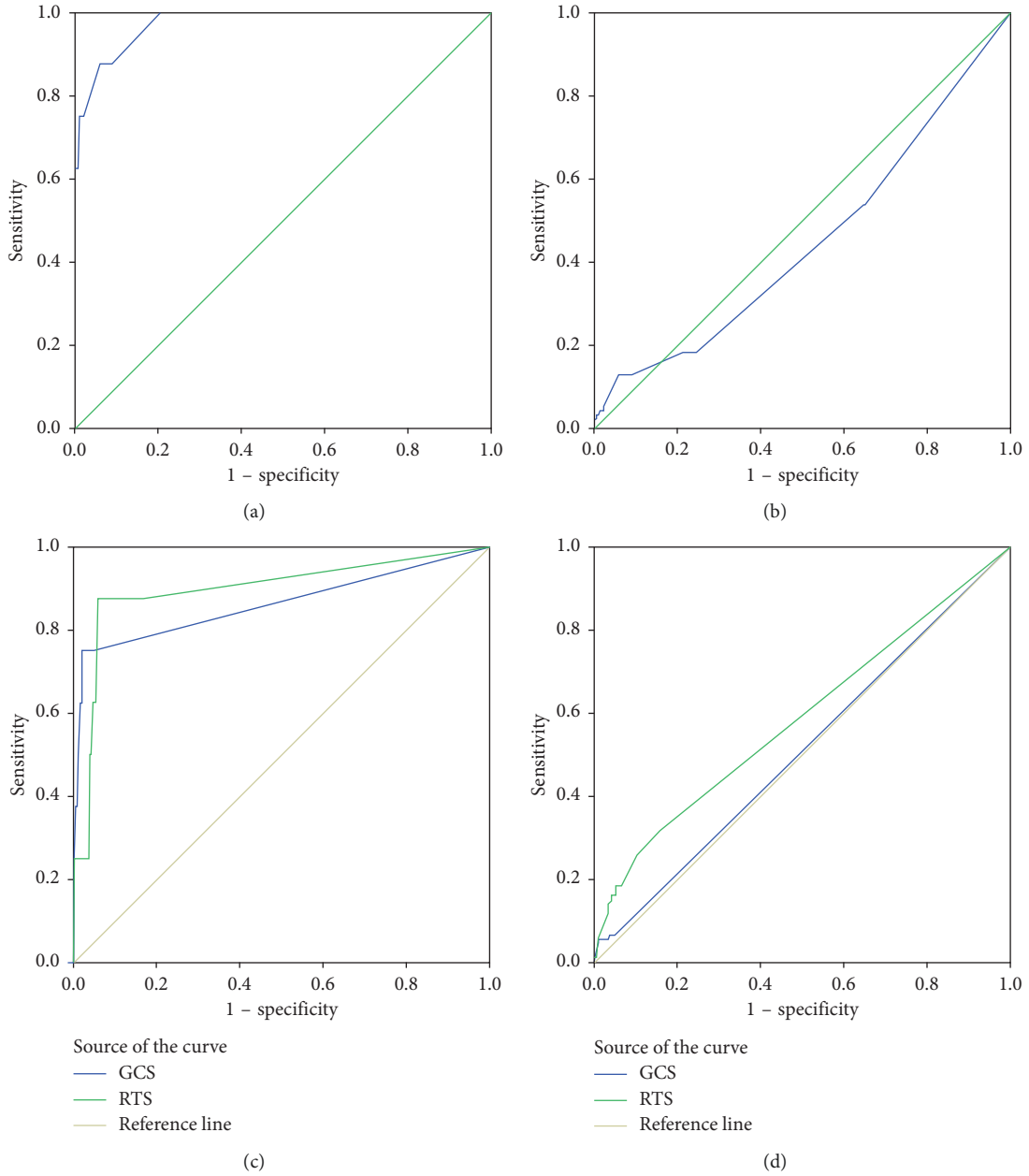

Figure 1: ROC curve of trauma scores to mortality and prolonged ICU stay. (a) ISS to mortality. (b) ISS to prolonged ICU stay. (c) GCS and RTS to mortality. (d) GCS and RTS to prolonged ICU stay.

Table 4: AUC value of trauma score to mortality and prolonged ICU stay.

	Mortality			Prolonged ICU stay		
	AUC	Std. error	95% CI	AUC	Std. error	95% CI
ISS	0.975	0.018	0.940~1	0.448	0.033	0.384~0.513
GCS	0.864	0.093	0.682~1	0.509	0.032	0.447~0.572
RTS	0.899	0.071	0.759~1	0.587	0.034	0.520~0.653

prolonged ICU stay from high-risk ones and may improve ED disposition in clinical practice. Very few studies have investigated trauma scoring and prognosis for young children under the age of 7 years. Further research on the association of trauma scores with prognosis in specific types of accidents is needed in the future.

Table 5: Association of trauma score's cutoff value with mortality.

		Number	Mortality rate N (%)	p-value	Odds ratio
ISS	ISS ≥ 15	63	7 (11.1%)	< 0.001	109.25
	ISS < 15	875	1 (0.1%)		
GCS	GCS ≤ 11	26	6 (23.1%)	< 0.001	136.50
	GCS > 11	912	2 (0.2%)		
RTS	RTS ≤ 7	71	7 (9.9%)	< 0.001	94.72
	RTS > 7	867	1 (0.1%)		

6. Conclusion

In this study, we found that worse trauma scores of ISS, GCS, and RTS were associated with increased mortality, prolonged ICU stays, and HLOS among young children's injuries. Among these three trauma scores, we found ISS to have the best predictive value. The cutoff values of ISS, GCS, and RTS for predicting mortality were 15, 11, and 7, respectively.

Data Availability

Raw data were generated at Chang Gung Memorial Medical Hospital. Derived data supporting the findings of this study are available from the corresponding author on request.

Conflicts of Interest

The authors hereby declare that they have no conflicts of interest in relation to this article.

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Research Article

Cognitive Impairment among Cardiac Arrest Survivors in the ICU: A Retrospective Study

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Background. Recent studies have presented the effects of cardiac arrest on long-term cognitive function and quality of life. However, no study has evaluated cognitive function in the early stage after regaining consciousness. *Purpose*. The objectives of this study were to analyse the incidence, clinical course, and associated factors of cognitive impairment of cardiac arrest survivors in intensive care unit (ICU). *Patients and methods*. We administered the Mini-Mental State Examination (MMSE) to cardiac arrest survivors who were treated with targeted temperature management (TTM) immediately after regaining consciousness. Patients whose MMSE scores indicated impaired cognitive function (MMSE < 24) were retested before ICU discharge. *Results*. In 92 patients, the median MMSE score was 21.0 (interquartile range (IQR), 16.0–24.0), and cognitive impairment was found in 64 patients. Fifty-three patients completed follow-up MMSEs, and the median scores were 20.0 (IQR, 13.5–23.0) for the first and 25.0 (IQR, 21.5–28.0) for the last test. Of the specific domains, recall (0.0 (IQR, 0.0–1.0) to 2.0 (IQR, 1.0–3.0)) and attention/calculation (3.0 (IQR, 1.0–4.0) to 4.0 (IQR, 2.0–5.0)) were the most affected domains until ICU discharge. The factors that were correlated with cognitive impairment on the last MMSE were older age (OR, 1.07 (95% CI, 1.01–1.14), $p = 0.016$), increased time to return of spontaneous circulation (ROSC) (OR, 1.08 (95% CI, 1.02–1.15), $p = 0.012$), and length of hospital stay (OR, 1.07 (95% CI, 1.00–1.14), $p = 0.044$). *Conclusions*. Cognitive impairments were common immediately after patients regained consciousness but recovered substantially before ICU discharge. Recall and attention/calculation still were impaired until ICU discharge, and older age, increased time to ROSC, and LOS were associated with this cognitive decline.

1. Introduction

Cardiac arrest is a major health problem [1] and has a yearly incidence of approximately 50–110 per 100000 people worldwide [2]. However, 30% to 50% of cardiac arrest survivors were reported to suffer from cognitive impairment [3]. Memory, attention, and executive functions were most affected [3, 4], followed by negative effects on participation/autonomy and on quality of life [5, 6]. Although targeted temperature management (TTM) has contributed to an overall increase in cardiac arrest survival and good neurological recovery over the past decade [7, 8], recent studies have presented that similar long-term cognitive impairments were found in cardiac arrest survivors treated with TTM [9, 10].

Regarding long-term cognitive impairments, there was a high heterogeneity for duration of follow-up between the studies [3, 9–11]. However, no study has evaluated cognitive function in the intensive care unit (ICU) early after regaining consciousness, and the process of cognitive function recovery has not been entirely presented. Further information on the quantification of recovery from cognitive impairment immediately after awakening would be important for counselling families in the ICU and useful as baseline for monitoring recovery progress in future interventional trials aimed at reducing cognitive impairment.

There are many of tools used to assess cognitive function after cardiac arrest but they are not yet standardized. Researchers use different tools as follows: one study used the

tools of the 41 Cent Test, the Montreal Cognitive Assessment (MoCA), and the Computer Assessment of Mild Cognitive Impairment [12] and the other study used a neuropsychological test battery including Cognitive-Log, Trail Making Test A and B, Verbal Fluency Test, Paragraph Recall Test Direct and Delayed, and the Adult Memory and Information Processing Battery Task A [13]. And, some group used other tools as follows: the Rivermead Behavioural Memory Test (RBMT), the Frontal Assessment Battery, and the Symbol Digit Modalities Test [9].

Among them, the Mini-Mental State Examination (MMSE) is a standardized tool for bedside assessment of overall cognitive function and was originally developed to screen for dementia and delirium [14]. The MMSE consists of a questionnaire that covers six cognitive domains. The maximum score is 30, and the score differs greatly depending on the educational level or age of the subject, but generally, values below 24 indicate cognitive impairment [14]. Sometimes, the MMSE is used as a screening instrument for cognitive impairment in cardiac arrest survivors because it is simple, widely used, and practical for serial use, and the validity of the MMSE is well established [5, 15, 16]. We administered the MMSE to TTM-treated cardiac arrest survivors who regained consciousness. The patients who presented impaired cognitive function were retested later during ICU care.

The aim of this study was to analyse the incidence and clinical course of cognitive impairment in TTM-treated survivors who regained consciousness during intensive care. We also evaluated the associating factors for early cognitive impairment, especially the degree of neurological injury using serum biomarker in these patients.

2. Methods

We conducted a retrospective analysis of one tertiary hospital TTM registry and collected adult cardiac arrest patients (>18 years old) treated with TTM starting in 2009. During study period, a total of patients who regained consciousness after TTM between March 2009 and June 2017 were recruited. We excluded patients who did not undergo the MMSE during the admission period. The study was approved by our Institutional Review Board and was conducted with a waiver of patient consent because of the noninterventional, retrospective design of the study.

2.1. TTM and Sedatives Protocol. During the study period, postcardiac arrest care including TTM was performed according to the guidelines that were current at the time of treatment [17, 18]. Once a patient achieved return of spontaneous circulation (ROSC), the patient was considered eligible for TTM at 33°C, which was initiated as soon as possible after ROSC regardless of the initial cardiac rhythm or arrest location. In our TTM protocol, midazolam (0.08 mg kg^{-1} intravenously) was immediately administered during induction to control shivering followed by a continuous midazolam infusion (0.04–0.2 mg kg^{-1} h^{-1}). After completion of the 24-h maintenance period, controlled rewarming at a rate of 0.25°C h^{-1} was performed until the core temperature reached 36.5°C. Midazolam dosage was reduced during rewarming and stopped before reaching normal body temperature.

2.2. MMSE Measures and Other Variables. According to our protocol, after patients who presented good neurological function were extubated, time at which a meaningful MMSE could be conducted; cognitive function was assessed by ICU physicians. Individuals with an endotracheal tube or who were essentially muted did not undergo an MMSE. In this study, the MMSE standardized in Korean was used [19]. The MMSE consists of a thirty-point scale (range 0–30; 30 = max) that assesses six different cognitive elements or domains: (1) orientation to time (range 0–5), (2) orientation to place (range 0–5), (3) three word registration (range 0–3), (4) attention/calculation counting backwards by seven (range 0–5), (5) delayed recall of the three words (range 0–3), and (6) language involving comprehension of a three-step command, naming, repetition, and sentence writing (range 0–8), and visuoconstruction involving the copy of intersecting pentagons (range 0–1). Whenever possible, MMSE in cognitively impaired patients (MMSE < 24) was reassessed by same physician on ICU discharge day.

Demographic information, resuscitation variables, and comorbidities such as coronary artery disease (CAD), hypertension, and diabetes mellitus (DM) were analysed from the patient registry. We also evaluated some confounding variables for MMSE score. The total dose of midazolam administered to patients during TTM was analysed. The time to MMSE was defined as the median number of hospital days on which the MMSE was conducted, and the time to obey was recorded when the patient gave a meaningful response to verbal commands.

During study period, neuron-specific enolase (NSE) and S100 calcium-binding protein B (S100B) were measured as standard tests. Initial measurements of NSE and S100B were obtained as soon as possible after ROSC, and these measurements were repeated 24, 48, and 72 h later based on time of ROSC. The serum was analysed with Roche Elecsys NSE and S100 reagents (Roche Diagnostics, Mannheim, Germany). If the serum showed significant haemolysis, the results for NSE were discarded. The upper limits of normal serum levels for NSE and S100B were determined by our laboratory as 14.7 ng mL^{-1} and 0.105 ng mL^{-1}, respectively.

2.3. Statistical Analysis. All data are summarized and displayed as the mean ± standard deviation or median with interquartile range (IQR) for continuous variables and as the number (percentage) of patients in each group for categorical variables. Patients were separated by their MMSE scores from the first and last measurements into cognitively impaired (MMSE < 24) and cognitively intact (MMSE ≥ 24) groups. Comparisons of categorical variables between groups were made using either χ^2 test or Fisher's exact test as appropriate. In addition, continuous variables were compared between groups using t tests or Mann–Whitney U tests. Associated factors were evaluated using multivariate

logistic regression analyses, and odds ratios (ORs) with 95% confidence intervals (CIs) were estimated in the logistic regression models. For repeated measurements, the Wilcoxon signed-rank test was used. All analyses were performed using SPSS 24.0 software (IBM, SPSS Inc., Chicago, IL, USA). A value of $p < 0.05$ was considered significant for all analyses.

3. Results

During the study period, a total of 1280 adult patients were attempted cardiopulmonary resuscitation. Of these, 569 patients regained spontaneous circulation and 317 patients (55.7%) underwent TTM (Figure 1). Of these patients, 212 patients did not regain consciousness, and 13 patients were excluded because of ICU discharge before MMSE examination ($n = 6$), poor neurologic status ($n = 4$), or missing data ($n = 3$). Finally, 92 patients were included in this study. The baseline demographics, comorbidities, resuscitation variables, and outcomes of the patients are summarized in Table 1. The mean age was 46.1 ± 15.0 years, and sixty-three patients (68.5%) were males. A total of 79 patients (85.9%) had a witness present during cardiac arrest, and 61 patients (66.3%) received cardiopulmonary resuscitation by bystanders. In the first monitored rhythm, a shockable rhythm was identified in 66 patients (71.7%). The mean time from arrest to ROSC was 21.5 ± 13.9 minutes. Twenty-eight patients had scores ≥24 on the initial MMSE, and their median MMSE score was 25.5 (IQR, 24.0–28.0). Of the 64 cognitively impaired patients, 53 patients underwent a follow-up MMSE in the ICU.

3.1. MMSE Scores Immediately after Regaining Consciousness. Figure 2 shows the time to obey and the time to the first MMSE in all participants. A meaningful response was presented by patients at a median time of day 3 (IQR, 3.0–3.0) of the hospital stay, and the first MMSE was administered at a median time of day 4 (IQR, 3.0–5.0) of the hospital stay. The median MMSE score was 21.0 (IQR, 16.0–24.0), and cognitive impairment (MMSE < 24) was found in 69.6% ($n = 64$) of patients. The median scores in each of the 6 domains were as follows: 2.0 for orientation to time (IQR, 1.0–3.0), 5.0 for orientation to place (IQR, 3.0–5.0), 3.0 for registration (IQR, 3.0–3.0), 3.0 for attention/calculation (IQR, 1.0–4.0), 1.0 for recall (IQR, 0.0–1.0), and 8.0 for language/visual construction (IQR, 7.0–9.0). The orientation to time, attention/calculation, and recall cognitive domains were more affected than the other domains.

3.2. Nature of Cognitive Recovery. A total of 53 patients completed follow-up tests, and their median scores were 20.0 (IQR, 13.5–23.0) and 25.0 (IQR, 21.5–28.0) for the first (at a median of 3 days [IQR, 3.0–4.0]) and last tests (at a median of 6 days [IQR, 5.0–8.0]), respectively. The difference between the two test scores was statistically significant ($p < 0.001$). In all 6 domains, a significant improvement in scores was observed (orientation to time: 2.0 [IQR, 0.3–3.0] to 4.0 [IQR, 2.3–5.0], $p < 0.001$; orientation to place: 4.0 [IQR, 3.0–5.0] to 5.0 [IQR, 5.0–5.0], $p < 0.001$; registration: 3.0 [IQR, 3.0–3.0] to 3.0 [IQR, 3.0–3.0], $p = 0.015$; attention/calculation: 3.0 [IQR, 1.0–4.0] to 4.0 [IQR, 2.0–5.0], $p < 0.001$; recall: 0.0 [IQR, 0.0–1.0] to 2.0 [IQR, 1.0–3.0], $p < 0.001$; language/visual construction: 8.0 [IQR, 6.0–9.0] to 9.0 [IQR, 8.3–9.0], $p < 0.001$; Figure 3). More than half of the patients recovered maximal scores in the orientation to place, registration, and language/visual construction domains. In contrast, attention/calculation and recall exhibited less recovery than the other cognitive domains.

3.3. Factors Associated with Cognitive Impairments. When all participants were divided by their initial MMSE scores into two groups, there was only a statistically significant difference between the groups in age at the time of cardiac arrest ($p = 0.020$; Table 1). We also divided the patients according to initial and last MMSE scores for patients who had a follow-up MMSE ($n = 53$) (Table 2). According to the dichotomization using the initial MMSE scores, there was no significant difference between the groups. On the other hand, for last MMSE score, the cognitively impaired group was significantly older than cognitively intact group (49.7 ± 13.4 years vs. 40.9 ± 12.6 years, $p = 0.023$). The time to ROSC and the time to the last MMSE were also longer in the cognitively impaired group than cognitively intact group ($p = 0.004$ and $p = 0.041$, respectively). Finally, the length of hospital stay in the cognitively impaired group was also longer than that of the cognitively intact group ($p = 0.013$).

To evaluate the independent predictors of cognitive impairment, we adjusted for age, time to ROSC, and LOS on the multivariate analysis (Table 3). In the analysis including all participants, age was significantly associated with cognitive impairment on the initial MMSE (OR, 1.04 [95% CI, 1.01–1.07], $p = 0.028$). In contrast, in the patients who also had a follow-up test, age was not associated with an initial lower MMSE score. Factors that were correlated with a lower MMSE score on the last MMSE were older age (OR, 1.07 [95% CI, 1.01–1.14], $p = 0.016$), increased time to ROSC (OR, 1.08 [95% CI, 1.02–1.15], $p = 0.012$), and LOS (OR, 1.07 [95% CI, 1.00–1.14], $p = 0.044$).

3.4. MMSE Score and Serum Biomarkers. NSE and the S100B serum levels were analysed as two groups that were divided according to each test time (Table 4). Scores from the first cognitive assessment were not associated with the biomarker levels. In contrast, the serum levels of both NSE and S100B at 24 h ($p = 0.030$ and $p = 0.022$, respectively) and of S100B at 48 h ($p = 0.009$) were significantly higher in the cognitively impaired group than in the cognitively intact group according to the last MMSE score.

4. Discussion

In our study, the incidence of cognitive impairment immediately after regaining consciousness, based on an initial MMSE score < 24, was 69.6%. In addition, we revealed that recall, orientation to time, and attention/calculation were initially the more impaired cognitive domains. Although the

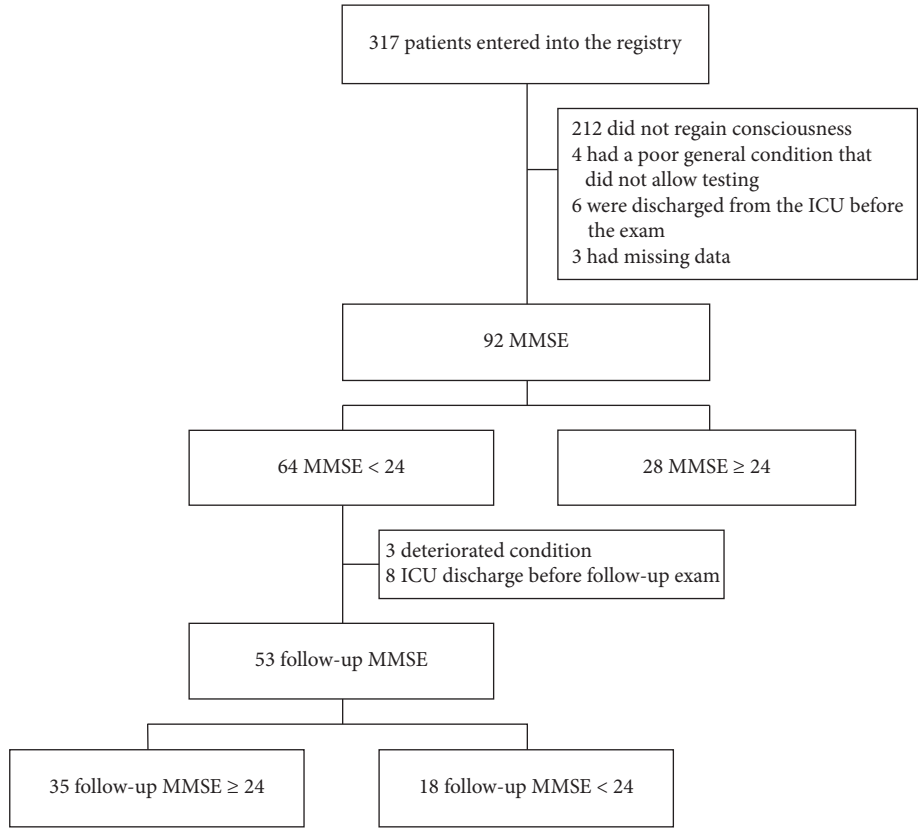

Figure 1: Flowchart of study inclusion.

Table 1: Patient characteristics and initial MMSE scores in total participants ($n = 92$).

	MMSE ≥ 24 ($n = 28$)	MMSE < 24 ($n = 64$)	p
Demographics			
Male	20 (71.4)	43 (67.2)	0.687
Age, years	40.6 ± 13.0	48.5 ± 15.3	0.020
Comorbidities			
CAD	3 (10.7)	7 (10.9)	0.975
CHF	1 (3.6)	1 (1.6)	0.543
Arrhythmia	0 (0.0)	3 (4.7)	0.244
Hypertension	4 (14.3)	13 (20.3)	0.493
Diabetes mellitus	0 (0.0)	5 (7.8)	0.128
Malignancy	0 (0.0)	1 (1.6)	0.506
OHCA	24 (85.7)	56 (87.5)	0.815
Cardiac cause	25 (89.3)	56 (87.5)	0.808
Shockable rhythm	22 (78.3)	44 (68.8)	0.336
Witnessed	25 (89.3)	54 (84.4)	0.534
Bystander CPR	21 (75.0)	40 (62.5)	0.243
Time to ROSC, min	19.6 ± 11.8	22.3 ± 14.8	0.396
Midazolam dose, mg*	271.1 (184.5–342.9)	222.8 (162.6–319.1)	0.242
Time to obey, day*	3.0 (2.3–3.0)	3.0 (3.0–3.0)	0.637
Time to exam, day*	4.0 (3.0–6.5)	4.0 (3.0–5.0)	0.449
Time interval from last midazolam to exam, day*	1.0 (0.0–3.8)	1.0 (0.0–2.0)	0.751
LOS, day*	11.5 (9.0–17.0)	14.5 (9.0–21.8)	0.377
MMSE score*	25.5 (24.0–28.0)	18.0 (13.3–21.0)	<0.001
Orientation to time	3.5 (3.0–4.0)	1.5 (0.3–3.0)	<0.001
Orientation to place	5.0 (4.3–5.0)	4.0 (3.0–5.0)	0.006
Registration	3.0 (3.0–3.0)	3.0 (3.0–3.0)	0.011
Attention/calculation	4.0 (3.3–5.0)	1.0 (0.3–3.0)	<0.001
Recall	2.0 (1.0–3.0)	0.0 (0.0–1.0)	<0.001
Language/visual construction	9.0 (9.0–9.0)	8.0 (6.0–9.0)	<0.001

*Median (interquartile range); MMSE, Mini-Mental State Examination; OHCA, out-of-hospital cardiac arrest; CAD, coronary artery disease; CHF, congestive heart failure; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; LOS, length of hospital stay.

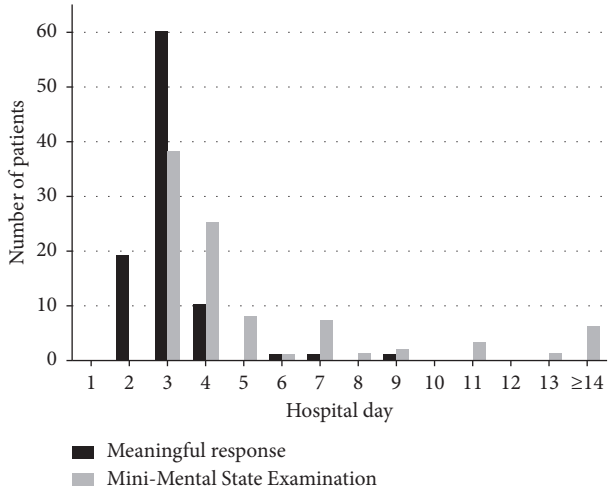

Figure 2: Time to meaningful response and first Mini-Mental State Examination among the participants.

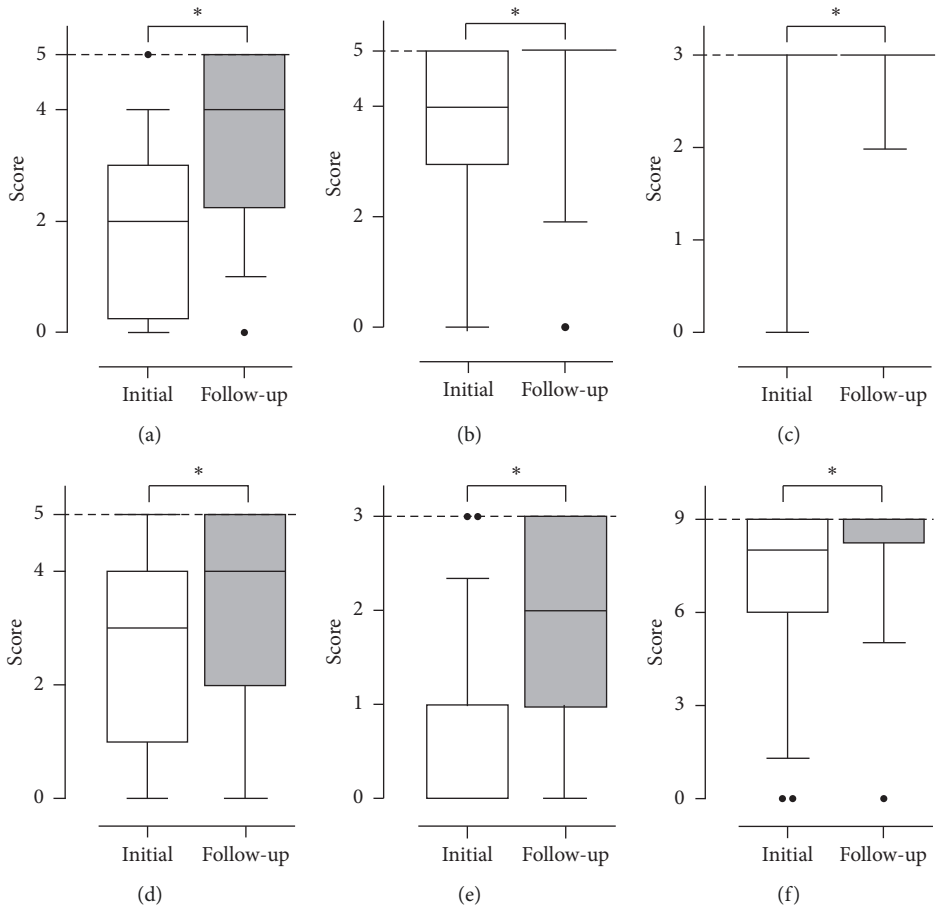

Figure 3: Changes in the score of each domain of Mini-Mental State Examination at 2 different time points ($n = 53$). Bars represent the median values, boxes represent the interquartile range, and whiskers extend to the 5th and 95th percentiles. Dashed lines indicate the maximal score of each domain. $^{*}p < 0.05$. (a) Orientation to time. (b) Orientation to place. (c) Registration. (d) Attention/calculation. (e) Recall. (f) Language/visual construction.

follow-up MMSE showed that these domains recovered substantially, the recall and attention/calculation domains still were impaired even before ICU discharge. Age and time to ROSC were independent predictors of cognitive impairment on the follow-up MMSE, which was associated with high serum biomarker levels.

Table 2: Patient characteristics according to first and last MMSE scores among participants with a follow-up MMSE ($n = 53$).

	Initial MMSE score			Last MMSE score		
	MMSE ≥ 24 ($n = 12$)	MMSE < 24 ($n = 41$)	p	MMSE ≥ 24 ($n = 35$)	MMSE < 24 ($n = 18$)	p
Demographics						
Male	7 (58.3)	29 (70.7)	0.418	23 (65.7)	13 (72.2)	0.631
Age, years	42.6 ± 12.2	44.3 ± 13.9	0.698	40.9 ± 12.6	49.7 ± 13.4	0.023
Comorbidities						
CAD	1 (8.3)	4 (9.8)	0.882	4 (11.4)	1 (5.6)	0.488
CHF	0 (0.0)	1 (2.4)	0.585	1 (2.9)	0 (0.0)	0.469
Arrhythmia	0 (0.0)	3 (7.3)	0.335	1 (2.9)	2 (11.1)	0.218
Hypertension	3 (25.0)	5 (12.2)	0.276	5 (14.3)	3 (16.7)	0.819
Diabetes mellitus	0 (0.0)	1 (2.4)	0.585	1 (2.9)	0 (0.0)	0.469
Malignancy	0 (0.0)	1 (2.4)	0.585	1 (2.9)	0 (0.0)	0.469
OHCA	10 (83.3)	38 (92.7)	0.330	31 (88.6)	17 (94.4)	0.488
Cardiac cause	10 (83.3)	38 (92.7)	0.330	33 (94.3)	15 (83.3)	0.196
Shockable rhythm	8 (66.7)	31 (75.6)	0.537	28 (80.0)	11 (61.1)	0.140
Witnessed	10 (83.3)	32 (78.0)	0.691	29 (82.9)	13 (72.2)	0.366
Bystander CPR	9 (75.0)	23 (56.1)	0.239	23 (65.7)	9 (50.0)	0.268
Time to ROSC, min	15.6 ± 8.3	20.6 ± 12.7	0.207	16.1 ± 11.7	25.9 ± 9.9	0.004
Midazolam dose, mg*	236.3 (184.5–286.3)	239.7 (170.9–344.4)	0.774	242.0 (190.7–342.8)	208.6 (133.6–342.2)	0.419
Time to obey, day*	3.0 (2.0–3.0)	3.0 (3.0–3.0)	0.151	3.0 (3.0–3.0)	3.0 (3.0–3.0)	0.335
Time to exam, day*	3.5 (3.0–4.0)	3.0 (3.0–4.0)	0.981	5.0 (5.0–7.0)	7.0 (5.0–12.5)	0.041
Time interval from last midazolam to exam, day*	1.0 (0.0–1.8)	1.0 (0.0–1.0)	0.901	2.0 (2.0–4.0)	5.0 (2.0–10.3)	0.011
LOS, day*	11.5 (9.0–16.3)	15.0 (9.5–21.0)	0.139	13.0 (9.0–17.0)	16.0 (13.0–34.5)	0.013

*Median (interquartile range).

Table 3: Independent predictors for cognitive impairment (MMSE < 24).

	All participants ($n = 92$)		Participants with follow-up MMSE ($n = 53$)			
			Initial MMSE score		Last MMSE score	
	Adjusted OR† (95% CI)	p	Adjusted OR† (95% CI)<	p	Adjusted OR† (95% CI)	p
Age, years	1.04 (1.01–1.07)	0.025	1.01 (0.96–1.06)	0.750	1.07 (1.01–1.14)	0.016
Time to ROSC, min	1.01 (0.98–1.05)	0.498	1.03 (0.96–1.10)	0.433	1.08 (1.02–1.15)	0.012
LOS, day	1.02 (0.98–1.06)	0.298	1.07 (0.97–1.19)	0.181	1.07 (1.00–1.14)	0.044

†ORs are adjusted for age, time to return of spontaneous circulation, and time to cognitive assessment. MMSE, Mini-Mental State Examination; OR, odds ratio; CI, confidence interval; ROSC, return of spontaneous circulation.

Table 4: Comparison of serum biomarkers between patients with and without cognitive impairment ($n = 53$).

	First cognitive assessment			Last cognitive assessment		
	MMSE ≥ 24 ($n = 12$)	MMSE < 24 ($n = 41$)	p	MMSE ≥ 24 ($n = 35$)	MMSE < 24 ($n = 18$)	p
NSE 0 h, ng/mL ($n = 48$)	22.03 (15.30–31.52)	18.59 (15.08–22.80)	0.206	19.09 (13.84–23.05)	20.05 (16.85–26.66)	0.301
NSE 24 h, ng/mL ($n = 45$)	19.94 (15.67–24.10)	19.20 (15.16–22.27)	0.653	17.86 (14.95–21.80)	21.40 (18.02–26.19)	0.030
NSE 48 h, ng/mL ($n = 37$)	11.27 (7.66–17.48)	12.40 (8.17–17.33)	0.604	11.58 (7.98–17.44)	15.20 (7.86–17.29)	0.425
NSE 72 h, ng/mL ($n = 23$)	9.70 (8.01–19.86)	11.29 (10.51–12.90)	0.804	10.78 (8.30–13.85)	13.64 (11.09–13.65)	0.315
S100B 0 h, ng/mL ($n = 51$)	0.27 (0.18–1.62)	0.29 (0.15–0.95)	0.464	0.23 (0.17–0.67)	0.37 (0.15–1.75)	0.411
S100B 24 h, ng/mL ($n = 51$)	0.08 (0.06–0.09)	0.09 (0.06–0.11)	0.484	0.07 (0.05–0.10)	0.09 (0.07–0.13)	0.022
S100B 48 h, ng/mL ($n = 46$)	0.07 (0.06–0.10)	0.10 (0.06–0.12)	0.395	0.07 (0.06–0.11)	0.11 (0.08–0.15)	0.009
S100B 72 h, ng/mL ($n = 25$)	0.07 (0.04–0.08)	0.06 (0.04–0.09)	0.912	0.06 (0.04–0.08)	0.08 (0.06–0.11)	0.111

MMSE, Mini-Mental State Examination; NSE, neuron-specific enolase; S100B, S100 calcium-binding protein B.

In our results, the early time course of cognitive dysfunction was dynamic. Although more than two-thirds of all patients had scores <24 on the initial MMSE, a significant overall improvement was observed from the initial to the final MMSE among patients who underwent a follow-up test. The change in MMSE score was a 5-point increase over 3 days (median values). Finally, more than two-thirds had scores ≥24 points. This clinical course of early-phase cognitive impairment would be important information for counselling families.

Significant differences among the initial scores of each MMSE domain were also observed. Memory function, particularly recall, was preferentially impaired. The functions of orientation to time and attention/calculation were

moderately to severely impaired. Although these declines recovered substantially over a short period, the recall and attention/calculation domains were still impaired even before ICU discharge.

Traditionally, the MMSE was used as a screening instrument for cognitive impairment in ICU [5, 15, 16]. Although recently MoCA is used as representative congitive exam in cardiac arrest survivors, the MoCA took nearly twice as longer to perform than the MMSE [20], and patients who cannot satisfactorily complete the MMSE are likely to experience unnecessary stress while completing more in-depth and intense exams [12]. Therefore, Koller et al. [12] presented that MMSE testing should still be utilized as a screening tool prior to the administration of exams such as the MoCA. We also believed that it is appropriate to use the MMSE to screen cognitive function immediately after regaining consciousness and to evaluate clinical course of cognitive impairment in a short period.

Brain anoxia after cardiac arrest causes severe brain injury in survivors. To the best of our knowledge, the present study is the first clinical report to describe the quantitative association between cognitive impairment and time to ROSC in patients treated with TTM. Following a brief period of circulatory arrest, a patient may be transiently confused or may develop a severe Korsakoff-like amnesic state with profoundly impaired recall and recognition abilities but a retained short-term memory [21]. Amnesia following cardiac arrest is associated with limited lesions affecting the bilateral hippocampus with little cortical damage [22, 23]. Recovery after a prolonged arrest is associated with intellectual deficits, including disorders of attention, orientation, insight, and judgement [24]. In our results, increasing time to ROSC was correlated with cognitive impairment on the last MMSE (at a median time of hospital day 6).

Most of the previous investigations of the incidence of cognitive decline after cardiac arrest assumed that impairments were specifically related to brain anoxia. However, brain anoxia may not be the only or even the predominant cause of mild cognitive impairment that is observed during ICU care. In addition to neuronal injury by hypoxic insult, another possible cause is the use of sedatives during TTM. In the setting of hypothermia, decreased metabolic activity is also believed to delay the clearance of sedatives [18]. Interestingly, our results showed that the total administered dose of midazolam was not different between cognitively impaired and intact groups. Moreover, different serum levels of biomarkers between groups according to last cognitive function shows that neuronal injury may play a role in these cognitive impairments, which is consistent with the previous literature [25]. Grubb et al. investigated the prognostic value of serum protein S100B and NSE concentrations for predicting memory impairment using RBMT at discharge and reported that correlation coefficients for RBMT score versus serum S100B levels, especially between 24h and 48 h after ROSC was significant [25].

On the other hand, the immediate cognitive dysfunction was lesser likely to be associated with hypoxic brain injury and it suggests that there may be another explanation for the immediate cognitive decline. In not only postcardiac arrest patients but also postoperative patients, cognitive declines were commonly observed [26]. Microemboli released during the surgery have been widely assumed to be the principal cause, but few studies have shown a robust correlation between the number of emboli and cognitive outcomes [27]. Although the pathophysiology of postoperative cognitive dysfunction remains poorly understood, it is considered to be a multifactorial process by nonspecific stress [26, 27]. Like this, it could be hypothesized that nonspecific multifactorial effects of major stress, including chest compression, medications, hypothermia, and artificial ventilation, might also be contributing factors to initial cognitive decline in our cohort.

Lilja et al. recently reported that similar levels of cognitive impairment were found in cardiac arrest survivors treated with TTM and a matched control group of ST-segment-elevation myocardial infarction patients who had the same cardiovascular risk factors [9]. In studies of patients who underwent coronary artery bypass grafting (CABG) and matched controls, the intervention itself was not responsible for the cognitive impairment, and the initial decline of cognitive function reflected a more severe stage of the underlying cardiac disease necessitating CABG [27]. Our cohort was composed of relatively young patients who had relatively low frequencies of these comorbidities such as hypertension, DM, and CAD. Although no differences were observed regarding comorbidities between the two groups, we could not clarify the impact of the cardiovascular burden on cognitive impairment in this study.

Many who achieved ROSC will suffer from the post-cardiac arrest syndrome, a highly inflammatory state characterized by reperfusion injury and oxidative stress, and it affects not only brain injury but also multiorgan dysfunction [28]. Moreover, TTM has an impact on all biological processes. Infection including sepsis, acute kindey injury, electrolyte abnormalities was reported as adverse events during intensive care of these patients [29]. These general conditions may affect cognitive function and consequentially MMSE score. Although our retrospective study could not analyse these conditions as confounder, we believed that the association of longer LOS with last cognitive dysfunction might be due to these conditions.

Our cognitive assessments were conducted in a short period, and there are several limitations to interpreting the results. The first limitation is that this study was a retrospective, registry-based study, which may decrease the generalizability of the results. MMSE was not performed for all consciousness survivors. In addition, a follow-up test was not performed in some patients with cognitive dysfunction. Although midazolam dosage was reduced during rewarming and stopped before reaching normal body temperature, there was no further detailed protocol. Thus, the results become difficult to interpret and generalize. Second, our results were analysed without knowledge of the baseline cognitive functions of the participants. The educational levels of patients, including the average number of years attending school, was not considered a confounding variable, and neuropsychiatric comorbidities such as previous stroke, cognitive impairment, and other psychiatric

disorder, which would have impact on the MMSE more than cardiovascular comorbidities, were also not evaluated. We did not evaluate cognitive complaints via subjective questionnaires or questionnaires from the partners. A subjective sense of cognitive decline cannot be detected by standardized neuropsychological testing, and such self-reported cognitive symptoms most commonly involve memory, which was the most affected domain in our results. Third, in some delayed awakening patients, sedatives were used for critical care after TTM, but we could not adjust the analyses to control for sedative administration. Thus, the results of this study should be cautiously interpreted, and a further prospective study including various cognitive function tests is needed to increase the generalizability of our results.

5. Conclusion

In this study conducted in the ICU, more than two-thirds of the survivors exhibited cognitive impairment immediately after regaining consciousness, based on an MMSE score < 24. In addition, the impaired cognitive domains identified from the MMSE were recall, orientation to time, and attention/calculation. The follow-up MMSE showed that these domains recovered substantially, but some patients still had impaired cognitive function in the recall and attention/calculation domains even before ICU discharge. Older age, the time to ROSC, and LOS seemed to be associated with cognitive impairment on the follow-up MMSE.

Data Availability

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

Ethical Approval

The study was approved by the Institutional Review Board of the Catholic University of Korea at Seoul Saint Mary's Hospital and conducted with a waiver of patient consent because of the noninterventional, retrospective design of the study.

Disclosure

This abstract was presented in EACEM 2018.

Conflicts of Interest

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

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Research Article

Comparison of i-Gel as a Conduit for Intubation between under Fiberoptic Guidance and Blind Endotracheal Intubation during Cardiopulmonary Resuscitation: A Randomized Simulation Study

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Purpose. This study aimed to compare intubation performances among i-gel blind intubation (IGI), i-gel bronchoscopic intubation (IBRI), and intubation using Macintosh laryngoscope (MCL) applying two kinds of endotracheal tube during chest compressions. We hypothesized that IGI using wire-reinforced silicone (WRS) tube could achieve endotracheal intubation most rapidly and successfully. *Methods*. In 23 emergency physicians, a prospective randomized crossover manikin study was conducted to examine the three intubation techniques using two kinds of endotracheal tubes. The primary outcome was the intubation time. The secondary outcome was the cumulative success rate for each intubation technique. A significant difference was considered when identifying $p < 0.05$ between two devices or $p < 0.017$ in post hoc analysis of the comparison among three devices. *Results*. The mean intubation time using IGI was shorter ($p < 0.017$) than that of using IBRI and MCL in both endotracheal tubes (17.6 vs. 29.3 vs. 20.2 in conventional polyvinyl chloride (PVC) tube; 14.6 vs. 27.4 vs. 19.9 in WRS tube; sec). There were no significant ($p < 0.05$) differences between PVC and WRS tubes for each intubation technique. The intubation time to reach 100% cumulative success rate was also shorter in IGI ($p < 0.017$) than that in IBRI and MCL in both PVC and WRS tubes. *Conclusions*. IGI was an equally successful and faster technique compared with IBRI or MCL regardless of the use of PVC or WRS tube. IGI might be an appropriate technique for emergent intubation by experienced intubators during chest compressions.

1. Introduction

Airway management in cardiac arrest is essential for successful resuscitation [1]. Globally, i-gel has been used as a popular supraglottic airway device (SAD) for out-of-hospital cardiopulmonary resuscitation (CPR) [2, 3]. Most SADs except i-gel have a time-consuming process of inflating balloon. However, i-gel does not need to inflate balloon, an advantage which could be beneficial to reduce the time to first ventilation [4]. Recently, i-gel has been widely used, and we frequently encounter out-of-hospital cardiac arrest (OHCA) patients who are already i-gel inserted on arrival to the emergency department.

In CPR for OHCA patients, advanced airway device insertions such as SAD or endotracheal intubation (ETI) are not prior to chest compressions (CCs). When CCs are performed properly, advanced airway device insertion should be considered for optimal oxygenation. Especially in OHCA caused by serious respiratory causes such as acute respiratory distress syndrome or airway obstruction, ETI can be more appropriate than SAD insertion to correct hypoxia and to improve survival ultimately [5].

Nevertheless, ETI using direct laryngoscope during CPR could not be easily achieved even if it is performed by experienced emergency physicians [6]. The vertical motion of glottis caused by CCs interferes in accurate ETI, which can

increase hands-off time in CPR [7]. To minimize hands-off time and perform ETI rapidly and accurately, we thought ETI through inserted i-gel could be more advantageous than using direct laryngoscope during CPR.

ETI through inserted i-gel has already been attempted by anesthesiologists in the form of fiberoptic bronchoscope-guided ETI [8–10]. However, it is not an easy technique to handle fiberoptic bronchoscopy for ETI during CPR even for the bronchoscopist. Recently, the novel ETI technique through i-gel without fiberoptic bronchoscope called i-gel blind intubation (IGI) has been introduced and attempted in operative intubation and prehospital resuscitation [11, 12].

We assumed that IGI could minimize interruptions of CCs and achieve successful ETI during CPR. In addition, when using conventional polyvinyl chloride (PVC) endotracheal tube (ETT) in IGI, the PVC tube can be folded and compressed when passing through i-gel. We thought it might result in an increase of hands-off time and decrease of ETI accuracy. So, we assume that the use of wire-reinforced silicone (WRS) tube instead of PVC tube could overcome this problem [13].

This study aimed to compare intubation performances among IGI, i-gel bronchoscopic intubation (IBRI), and intubation using Macintosh laryngoscope (MCL) applying two kinds of ETT during CCs. We hypothesized that IGI using WRS tube could achieve ETI most rapidly and successfully.

2. Methods

2.1. Study Design. We conducted a randomized crossover manikin study to examine intubation performance using two intubation techniques through i-gel (IGI and IBRI), direct laryngoscopy (MCL), and two ETTs during CCs. This study was performed at Hallym University's simulation center in February 2015. The local ethics committee approved this study in February 2015 (IRB Number: 2015-02-30; the institutional review board (IRB) of Hallym University Kangnam Sacred Heart Hospital). We registered the study protocol in Clinical Trials before study initiation (Clinicaltrials.gov: NCT02411422).

2.2. Participants. The sample size was calculated based on a previous study regarding the time required for intubation with CCs [11]. The intubation times (mean ± SD) using i-gel blind intubation was 24.0 ± 9.4 s. To detect a 33% difference in intubation time with a power of 0.9, we estimated that 22 operators would be adequate for each device with a 20% dropout rate. We recruited emergency physicians working at tertiary medical center in February 2015. The inclusion criteria were healthy volunteers (18–60 years) who had more than 50 experiences of intubation using MCL and no experiences for IGI or IBRI. We excluded individuals with wrist or lower back disease. The verbal informed consents were obtained by the participants in this study because the waiver for the written informed consent was approved by the local IRB.

2.3. Equipment and Materials. We use direct laryngoscopy (Macintosh blade #4) and i-gel™ (Intersurgical, Workingham, UK, size 4), flexible intubation scope (Ambu® aScope™, Ambu co., Ballerup, Denmark) for ETI with fiberoptic guidance. We use two types of ETT, e.g., PVC tube (Mallinckrodt™ Hi-Lo Oral/Nasal Tracheal Tube Cuffed Murphy Eye, Covidien, Ireland #7.0) and WRS tube (Mallinckrodt™ Oral/Nasal ETT with TaperGuard™ cuff, Reinforced, Covidien, Ireland #7.0).

Participants performed IGI and IBRI using size-4 i-gel (Intersurgical, Workingham, UK) for medium adult (50–90 kg). A flexible intubation scope was used to guide ETT in IBRI. For direct laryngoscope, Macintosh blade (MCL) was used; this device has a size-4 curved blade with a Satin Slip Stylet (Mallinckrodt Medical, St. Louis, MO, USA). Two types of ETTs with an internal diameter of 7.0 mm were used in this study.

We used a high-fidelity manikin (ALS simulator, Laerdal, Stavanger, Norway) to perform CCs and ETI. The normal (nondifficult) airway setting was maintained in the manikin during the study.

The bed-height setting of this study was simulated using a bed (Transport stretcher® No. 747, 76 × 211 cm, 228 kg, Stryker Co., Kalamazoo, MI, USA) with a foam mattress (66 × 192 × 7.6 cm, soft foam with polyurethane covering, Stryker Co., Kalamazoo, MI, USA). A backboard (45 × 60 × 1 cm, 3 kg Lifeline Plastic, Sung Shim Medical Co., Bucheon, Korea) was placed on the bed. The height of the stretcher bed was adjusted to 88.6 cm (bed height: 80 cm + foam mattress: 7.6 cm + backboard: 1 cm) for both ETI and CCs.

2.4. Intervention. Instructors gave 1-hour lecture and 2-hour practice for high-quality CPR, ETI using i-gel as blind conduit (IGI), and ETI using i-gel as conduit with fiberoptic guidance (IBRI) for 23 subjects and 4 chest compressors. All instructors were advanced cardiovascular life support (ACLS) instructors certificated by AHA (American Heart Association). They also had more than 500 times experience for ETI and more than 50 times experience for IGI and IBRI. The CPR lecture was constituted with the appropriate chest compression (CC) rate (100–120 bpm), CC depth (5–6 cm), and complete chest recoil and avoiding hyperventilation. The lecture for IGI and IBRI was constituted with the method of i-gel insertion, how to use flexible intubation scope, and the confirmation method of successful intubation. In the IGI and IBRI practice, the subjects were required for more than 10 times drill for IGI and IBRI, respectively. The successful intubation was confirmed by chest rise during bag mask ventilation via ETT. All chest compressors during ETI were AHA-BLS providers. They performed 2 min high-quality CC during ETI on an ALS simulator to prevent fatigue. In the CPR practice, they were requested more than 5 times drill for 2 min hands-only CPR under guidance by ACLS instructors. The CPR quality was monitored by the feedback system of high-fidelity manikin.

After lecture and practice session, subjects were randomly divided into 2 groups by kinds of ETT firstly. For

dividing participants to 2 groups, we used drawing lots. The sequence generator (http://www.random.org) was used for random order generation in order to minimize learning effect.

We used two kinds of ETT, one was PVC tube with harder tip and the other was WRS tube with softer tip. Then, subjects rerandomized by a sequence of three ETI methods, i.e., direct laryngoscope, IGI, and IBRI. During ETI, certified basic life support (BLS) provider performed chest compression to the ALS simulator at a rate of 100 to 120 per minute and 5 to 6 cm depth with complete chest recoil. We use airway lubricant (Laerdal, Stavanger, Norway) when i-gel was used as a conduit for smooth insertion.

Instructor checked and recorded the time from the subject holding a handle of MCL or i-gel to when vocal cord exposed or i-gel was completely inserted (vocal cord exposure time, VET or i-gel insertion time, IIT), when ETT passed the vocal cord (tube pass time, TPT) and when 1st ventilation and chest rising were achieved through ETT by bagging bag-valve mask (1st ventilation time, FVT). (Figure 1).

In the procedure of IGI, subjects inserted i-gel to the ALS simulator, and then ETI was performed using i-gel as a blind conduit. In that order, the subject gave a ventilation through inserted ETT by bagging of bag-valve mask and verified chest rising. Before the subject performed IGI, instructors gave information for successful IGI such as sniffing position and counterclockwise rotation of ETT.

In the procedure of IBRI, we mounted an ETT #7.0 on the bronchoscope before the procedure began. Firstly, subjects inserted i-gel to the ALS simulator, and then subject inserted the bronchoscope to 15 mm connector of i-gel and checked the vocal cord while watching the screen monitor. Then, subjects passed the bronchoscope through vocal cord and verified carina. We pushed the mounted ETT through the bronchoscope and removed it and gave a ventilation through ETT with a bag-valve mask and verified chest rising.

When randomization of three kinds of ETI methods was finished, the subject performed ETI with another type of tube. The sequence of ETI methods was rerandomized.

All recordings were fulfilled by one instructor. We verified successful ETI by inserting the bronchoscope to ETT for visual, confirming carina.

2.5. Outcomes. We established intubation time as a primary outcome and cumulative intubation success rate as a secondary outcome.

We regarded esophageal intubation and exceeding 2 minutes from starting intubation to first ventilation as failed intubation. In all ETI attempts, verification of successful ETI using the bronchoscope was done.

2.6. Statistical Analysis. The data were collected and arranged using a standard spreadsheet application (Excel, Microsoft, Redmond, WA, USA). Statistical analysis was carried out with the 22.0 version of the Statistical Package for the Social Sciences (SPSS) program for windows (SPSS Inc., Chicago, IL, USA). We described statistics as frequencies and percentages for demographic data and

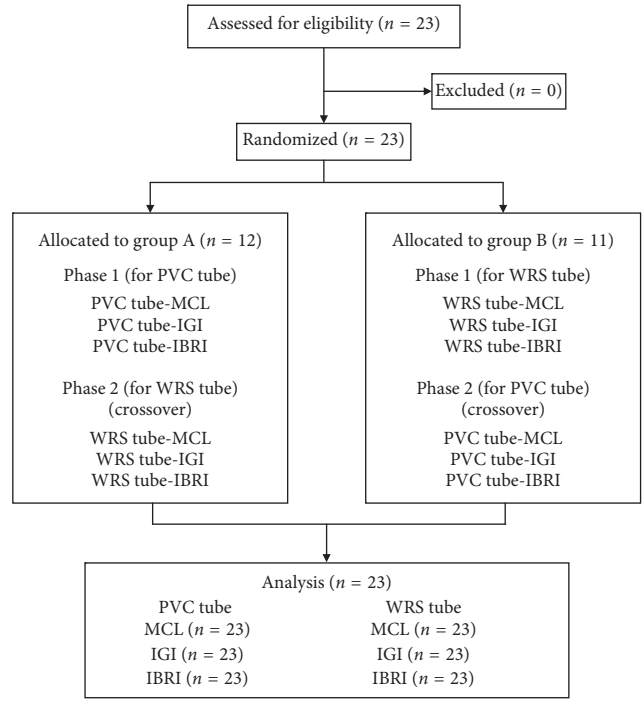

Figure 1: Flow diagram.

mean ± standard deviation (SD) for continuous data. We used the Shapiro–Wilk test for verifying normal distribution, and we used the Wilcoxon signed-rank test because the result was not according to normal distribution. In addition, we used the Friedman test for comparing three intubation methods and applied Bonferroni's method for post hoc analysis. Kaplan–Meier analysis was performed to analyze the cumulative success rate for intubation time. A significant difference was considered when p value was less than 0.05 between two devices and less than 0.017 was considered as significant difference in post hoc analysis of the comparison among three devices.

3. Results

Twenty-three subjects participated in this study. The baseline characteristics of the participants are shown in Table 1. ETI failures were recorded only three times in 138 attempts (2.1%), and these failures were all esophageal intubations. There were no cases exceeding 2 min intubation time.

3.1. i-Gel Insertion Time (IIT) or Vocal Cord Exposure Time (VET). IIT in IGI (4.1 ± 1.4 sec) was equal to that in IBRI (4.3 ± 1.2 sec) and significantly shorter than VET in MCL (5.8 ± 2.3 sec) regardless of kinds of ETT (IGI vs. IBRI, $p = 0.277$; IGI vs. MCL, $p = 0.001$). (Table 2).

3.2. Time from Vocal Exposure or i-Gel Insertion to Tube Pass (IIT-TPT). In the PVC tube, IIT-TPT in IGI (9.8 ± 8.4 sec) was significantly shorter than that of IBRI (20.0 ± 12.2 sec) and longer than that of MCL (7.0 ± 8.9 sec) (IGI vs. IBRI, $p = 0.001$; IGI vs. MCL, $p = 0.007$). In WRS tube, IIT-TPT

Table 1: Baseline characteristics.

	$N = 23$
Age, years	36.2 ± 5.4
Gender, male	19 (82.6%)
Intubators	
EM resident	8 (34.8%)
EP	15 (65.2%)
Experiences	
MCL ≥ 50 times	23 (100%)
i-Gel insertion ≥ 50 times	23 (100%)
Bronchoscopy ≥ 1 times	0 (0%)
IGI ≥ 1 times	0 (0%)
IBRI ≥ 1 times	0 (0%)

EM = emergency medicine; EP = emergency physician; MCL = Macintosh laryngoscopy; IGI = i-gel blind intubation; IBRI = i-gel bronchoscopic intubation.

in IGI (7.3 ± 2.3 sec) was equal to that in MCL (7.1 ± 4.0 sec) and shorter than that in IBRI (18.8 ± 17.5 sec) (IGI vs. MCL, $p = 0.314$; IGI vs. IBRI, $p < 0.001$). There were no differences between PVC and WRS tubes in the comparison of each of the three intubation techniques (MCL, $p = 0.098$; IGI, $p = 0.259$; IBRI, $p = 0.355$). (Table 3).

3.3. Time from Tube Pass to First Ventilation (TPT-FVT). In the PVC tube, TPT-FVT in IGI (3.3 ± 1.0 sec) was significantly shorter than that of IBRI (4.6 ± 0.9 sec) and MCL (7.0 ± 2.0 sec) (IGI vs. MCL, $p < 0.001$; IGI vs. IBRI, $p < 0.001$). Similarly, in WRS tube, TPT-FVT in IGI (3.3 ± 0.9 sec) was also shorter than that of IBRI (4.6 ± 2.0 sec) and MCL (7.0 ± 2.0 sec) (IGI vs. MCL, $p < 0.001$; MCL vs. IBRI, $p < 0.001$; IGI vs. IBRI, $p = 0.001$). There were no significant differences between PVC and WRS tubes in the comparison of each of the three intubation techniques (MCL, $p = 0.346$; IGI, $p = 0.348$; IBRI, $p = 0.291$). (Table 3).

3.4. First Ventilation Time (FVT, Total Intubation Time). In PVC tube, FVT in IGI (17.6 ± 8.9 sec) was shorter than that of IRBI (29.3 ± 12.5 sec) and MCL (20.2 ± 9.7 sec) (IGI vs. MCL, $p = 0.016$; IGI vs. IBRI, $p < 0.001$). In the WRS tube, FVT in IGI (14.6 ± 3.4 sec) was also shorter than that of IBRI (27.4 ± 19.1 sec) and MCL (19.9 ± 6.7 sec) (IGI vs. MCL, $p < 0.001$; IGI vs. IBRI, $p < 0.001$). There were no significant differences between PVC and WRS tube in the comparison of each of the three intubation techniques (MCL, $p = 0.426$; IGI, $p = 0.217$; IBRI, $p = 0.189$). (Table 3).

3.5. Cumulative Success Rate. In the comparisons of three intubation techniques, IGI showed significantly shortest time (about 20 seconds) to reach 100% cumulative success rate (IGI vs. MCL, $p = 0.002$; IGI vs. IBRI, $p < 0.001$). (Figure 2).

4. Discussion

This study demonstrated that the IGI was equally successful and faster technique compared with IBRI or MCL regardless of the use of PVC or WRS tube. To our knowledge, this is the first study which compares the intubation performance of IGI with that of IBRI during chest compressions.

According to the instruction manual for i-gel, IBRI is recommended for i-gel-guided intubation [14, 15]. IBRI may be advantageous to confirm intubation through camera images [16, 17]. However, suggested from the results of this study, to use IBRI, there were some problems. First, IBRI showed longest total intubation time (FVT) among three intubation techniques. It was because the time from i-gel insertion to ETT passing (TPT-FVT) in IBRI was significantly longer than that in IGI and MCL. Second, when attempting IBRI on manikin, participants often did not distinguish trachea from esophagus or they felt some resistance during ETT passing through the internal canal of i-gel. These experiences of participants suggest that intubators can incompletely confirm intubation by IBRI. Furthermore, since IGI and MCL showed equal intubation performance to IBRI, IBRI cannot be first option for emergent intubation during chest compressions.

The blind intubation through SAD such as IGI is not a usual method for emergent intubation in arrest patients [5]. Clinical physicians may select these blind intubations as a rescue technique for intubation failure regardless of the use of MCL or serious intubation conditions by massive blood or vomitus which is unavailable for video laryngoscopes [15, 16]. However, the camera image of IBRI or direct glottic view in MCL can be hindered by blood or vomitus of comatose patients [16]. Thus, IGI can be more appropriate than MCL and IBRI in these serious intubation conditions, because it is not related to camera image or direct vision. Although the intubation time of IGI may be not similar in real world, this study shows the possibility of IGI as a rescue option for arrest patients.

Regarding the nature of blind technique of IGI, the success rate for IGI has been reported from 75% to 100% despite the high speed of IGI [16, 18]. To improve the success rate of IGI, we need to apply counterclockwise rotation technique [11, 19]. This technique improved the success rate of IGI to 100%. Nevertheless, although this technique is applied for IGI in a clinical setting, we expect that the success rate will be lower than that of this study considering anatomical variation or hindrance by blood or vomitus of arrest patients.

In this study, we compared the efficacy of the PVC tube compared with that of the WRS tube in IGI and IBRI. The WRS tube can be more advantageous than the PVC tube, because the WRS tube is more flexible and noncompressible during the passage through i-gel [13, 20]. Nevertheless, the reinforced tube is expensive and less readily available compared with the PVC tube [17, 21]. This study demonstrates that 7 mm sized PVC tube shows similar intubation time compared with 7 mm WRS tube in IGI and IBRI. One previous study also reported that the use of the PVC tube showed lower incidence of postoperative complications including hemodynamic changes or hoarseness compared with those in the WRS tube [20]. Thus, in the clinical setting without the WRS tube, the PVC tube can be attempted for IGI or IBRI by experienced intubators.

Table 2: Comparisons of intubation time among three intubation techniques regardless of kinds of endotracheal tubes.

	MCL ($n = 23$)	IGI ($n = 23$)	IBRI ($n = 23$)	p value*	p value§ IGI vs. MCL	IBRI vs. MCL	IGI vs. IBRI
VET/IIT (sec)	6.1 ± 2.8	4.2 ± 1.3	4.4 ± 1.4	<0.001	<0.001	<0.001	0.12
TPT (sec)	13.2 ± 7.5	12.7 ± 6.4	23.8 ± 15.0	<0.001	0.59	<0.001	<0.001
FVT (sec)	28.0 ± 8.3	16.1 ± 6.7	28.4 ± 16.0	<0.001	<0.001	<0.001	<0.001
VET-TPT (sec)	7.0 ± 6.6	8.5 ± 6.1	19.4 ± 14.9	<0.001	0.008	<0.001	<0.001
TPT-FVT (sec)	6.8 ± 1.9	3.3 ± 1.0	4.6 ± 1.6	<0.001	<0.001	<0.001	<0.001

* $p < 0.05$ considered for significant difference by the Friedman test. § $p < 0.017$ considered for significant difference by the Wilcoxon signed-rank test using Bonferroni's correction. MCL = Macintosh laryngoscopy; IGI = i-gel blind intubation; IBRI = i-gel bronchoscopic intubation; VET = vocal cord exposure time; IIT = i-gel insertion time; TPT = tube pass time; FVT = first ventilation time.

Table 3: Comparisons of intubation time among three intubation techniques according to the kinds of endotracheal tubes.

		MCL	IGI	IBRI	p value§ MCL vs IGI	p value§ MCL vs IBRI	p value§ IGI vs IBRI
VET (IIT)	PVC	6.4 ± 3.2	4.3 ± 1.3	4.5 ± 1.6	0.002	0.002	0.205
	WRS	5.8 ± 2.3	4.1 ± 1.4	4.3 ± 1.2	0.001	0.009	0.277
	p value*	0.615	0.306	0.173			
TPT	PVC	13.5 ± 9.3	14.3 ± 8.3	24.7 ± 12.5	0.543	<0.001	0.001
	WRS	12.9 ± 5.3	11.2 ± 3.2	22.8 ± 17.3	0.173	<0.001	<0.001
	p value*	0.548	0.114	0.189			
FVT	PVC	20.2 ± 9.7	17.6 ± 8.9	29.3 ± 12.5	0.016	<0.001	0.001
	WRS	19.9 ± 6.7	14.6 ± 3.4	27.4 ± 19.1	<0.001	0.001	<0.001
	p value*	0.426	0.217	0.189			
VET-TPT	PVC	7.0 ± 8.6	9.8 ± 8.4	20.0 ± 12.2	0.007	<0.001	0.001
	WRS	7.1 ± 4.0	7.3 ± 2.3	18.8 ± 17.5	0.314	<0.001	<0.001
	p value*	0.098	0.259	0.355			
TPT-FVT	PVC	6.7 ± 1.8	3.3 ± 1.0	4.6 ± 0.9	<0.001	<0.001	<0.001
	WRS	7.0 ± 2.0	3.3 ± 0.9	4.6 ± 2.0	<0.001	0.001	0.001
	p value*	0.346	0.348	0.291			

§ $p < 0.017$ considered for significant difference by using Bonferroni's correction. * $p < 0.05$ considered for significant difference by the Wilcoxon signed-rank test in the comparison between PVC and WRS tubes. MCL = Macintosh laryngoscopy; IGI = i-gel blind intubation; IBRI = i-gel bronchoscopic intubation; VET = vocal cord exposure time; IIT = i-gel insertion time; TPT = tube pass time; FVT = first ventilation time; PVC = polyvinyl chloride endotracheal tube; WRS = wire-reinforced silicone endotracheal tube.

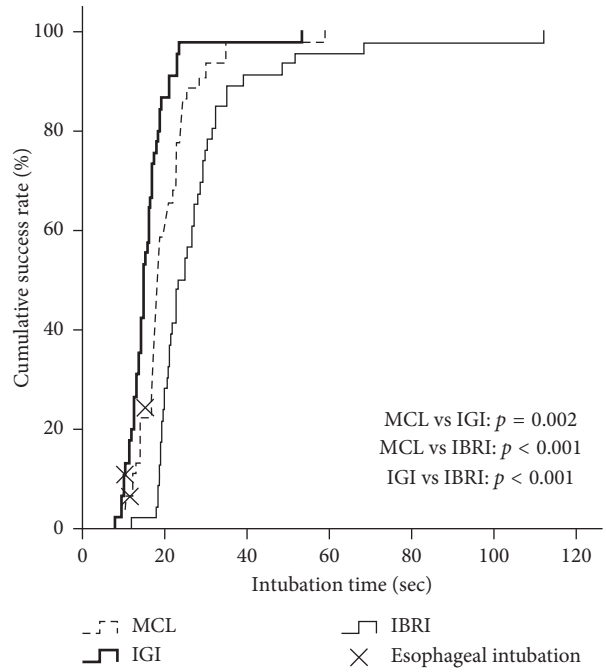

Figure 2: Comparisons of cumulative success rate among three intubation techniques regardless of kinds of endotracheal tubes.

This study has some limitations. First, the results of this study were based on manikin simulation. In a clinical setting, there will be several significant factors affecting the intubation performance. These factors include the dynamic hindrance for glottic view during chest compressions, the anatomical variation of airway, and the hindrance by blood or vomitus of arrest patients [16]. Thus, the results of this study may not be guaranteed in clinical situations.

Second, this study is a small sample pilot study for IGI and IBRI. Recently published regarding studies showed similar study design with this study [22–24]. Furthermore, the sample size of this manikin study might be not enough for clinical situation [25]. Therefore, to evaluate accurately the efficacy of IGI, further studies should be performed for humans in the clinical setting with large samples.

Third, although all participants had more than 50 times intubation experiences, the possibility of the experience difference still exists among junior and senior residents and EPs. These unequal experiences for intubation could affect the intubation performance such as intubation time or success rate.

5. Conclusion

IGI was an equally successful and faster technique comparing with IBRI or MCL regardless of the use of PVC or WRS tube. Therefore, IGI might be an appropriate technique for emergent intubation by experienced intubators during CCs.

Data Availability

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

Disclosure

This study was presented as a poster presentation in ESICM 2015 (A547) (https://icm-experimental.springeropen.com/articles/10.1186/2197-425X-3-S1-A547).

Conflicts of Interest

All authors declare that they do not have any potential conflicts of interest.

Authors' Contributions

HY Choi and W Kim contributed equally to this study.

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Research Article

Effect of the Floor Level on the Probability of a Neurologically Favorable Discharge after Cardiac Arrest according to the Event Location

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As the number of people living in high-rise buildings increases, so does the incidence of cardiac arrest in these locations. Changes in cardiac arrest location affect the recognition of patients and emergency medical service (EMS) activation and response. This study aimed to compare the EMS response times and probability of a neurologically favorable discharge among patients who suffered an out-of-hospital cardiac arrest (OHCA) event while on a high or low floor at home or in a public place. This retrospective analysis was based on Smart Advanced Life Support registry data from January 2016 to December 2017. We included patients older than 18 years who suffered an OHCA due to medical causes. A high floor was defined as ≥3rd floor above ground. We compared the probability of a neurologically favorable discharge according to floor level and location (home vs. public place) of the OHCA event. Of the 6,335 included OHCA cases, 4,154 (65.6%) events occurred in homes. Rapid call-to-scene times were reported for high-floor events in both homes and public places. A longer call-to-patient time was observed for home events. The probability of a neurologically favorable discharge after a high-floor OHCA was significantly lower than that after a low-floor OHCA if the event occurred in a public place (adjusted odds ratio (aOR), 0.58; 95% confidence intervals (CI), 0.37–0.89) but was higher if the event occurred at home (aOR, 1.40; 95% CI, 0.96–2.03). Both the EMS response times to OHCA events in high-rise buildings and the probability of a neurologically favorable discharge differed between homes and public places. The results suggest that the prognosis of an OHCA patient is more likely to be affected by the building structure and use rather than the floor height.

1. Introduction

Out-of-hospital cardiac arrest (OHCA) is a serious public health issue associated with poor outcomes [1]. Global incidence of this condition is high, and many countries have implemented programs and actions intended to improve the outcomes of affected patients [1, 2]. Previous studies have identified an association between survival after OHCA and emergency medical service (EMS) access time to patients, which is affected by the EMS system, ambulance density, and arrest location [3–5].

In 2018, 55% of the global population was estimated to reside in urban areas, and current projections suggest that this proportion will increase to 68% by 2050 [6]. Increases in population concentrations in urban areas have led to increases in the numbers of people who live in high-rise buildings. This demographic shift has exacerbated the issue of vertical patient access, as demonstrated by several studies reporting the negative outcomes of patients who experience OHCA in high-rise buildings. For example, significantly longer patient access times have been observed following ambulance calls for events that occurred ≥3 floors above ground, and an event site on a higher floor was associated with a lower 1-month neurologically favorable survival outcome after OHCA, compared to an event site on a lower floor [7, 8].

Despite the above findings, we did not assume that an increased vertical distance would always lead to a delayed EMS response time, as high-rise buildings tend to be densely populated and located in traffic centers. However, response times and patient outcomes might differ according to the structure of a high-rise building; a primarily residential building would have more independent spaces, compared to a public building. Therefore, this study aimed to compare the EMS response times and probability of a neurologically favorable discharge among patients who experienced an OHCA on a high floor (≥3 floors) in a home or in a public place.

2. Methods

2.1. Study Design and Setting. This retrospective cohort study was based on data included in the Smart Advanced Life Support (SALS) registry between January 2016 and December 2017. This is a prospective, population-based registry of OHCA cases that occurred in 18 urban and suburban areas in Korea, encompassing a total area of 7129.49 km^2 and total population of 11.6 million inhabitants.

2.2. Data Source. SALS is a method of advanced field resuscitation administered by paramedics under direct, video communication-based medical direction [9]. However, the SALS registry includes all data of cardiac arrest cases, regardless of whether direct medical direction was provided. The SALS data set includes patient variables, resuscitation status, and outcome variables according to the international Utstein style for cardiac arrest (CA). The patient variables included age, sex, and comorbidities. The resuscitation variables included the initial electrocardiographic rhythm, witnessed CA, bystander cardiopulmonary resuscitation (CPR), and response time. The outcome variables included a return of spontaneous circulation (ROSC), survival admission, and discharge with a Cerebral Performance Category (CPC) score [1, 2].

2.3. Study Population. Patients older than 18 years who suffered an OHCA due to medical causes were included in this study. Patients who were not resuscitated because of obvious signs of death, a refusal of CPR, a do-not-resuscitate (DNR) status, or medically directed cessation of CPR; those whose CA was witnessed by 911-initiated first responders; and those who had no data records for height of CA were excluded. Although bystander or emergency medical technicians started chest compressions if there were no obvious signs of death, resuscitation was not performed if it was stopped immediately by medical directors because this indicated no possibility of resuscitation.

2.4. Main Outcomes. The primary outcome was hospital discharge with a neurologically favorable outcome after an OHCA on a high ($\geq 3^{rd}$) floor in a home or public place. A neurologically favorable discharge was defined as a hospital discharge with a CPC score of 1 or 2 [10]. Additionally, we calculated the call-to-scene and call-to-patient times after OHCA for patients classified in the high-floor and low-floor ($<3^{rd}$) groups according to the CA event location. We further analyzed the factors related to a neurologically favorable discharge among these patients according to event location.

2.5. Measurements. A home was defined as an apartment, condominium, house, or townhouse. All other locations were considered public places. A high floor was defined as the 3^{rd} or higher floor above ground, while a low floor was defined as the 2^{nd} or lower floor above ground or below ground. The call-to-scene time was calculated as the time interval from the initial call to 911 to the vehicle stop. The call-to-patient time was calculated as the interval from the initial call to 911 to the time when the defibrillator was activated.

2.6. Statistical Analysis. Statistical analyses were performed using SPSS, version 24.0 (IBM Corp., Armonk, NY, USA). The patient and resuscitation characteristics and outcomes were compared between the high- and low-floor groups. Chi-square and Mann–Whitney *U* tests were used to compare categorical and continuous variables, respectively. A multivariate logistic regression analysis adjusted for sex, age, bystander CPR, witnessed arrest, and shockable initial rhythm was used to estimate the adjusted odds ratios (aORs) and 95% confidence intervals (CIs) of clinical outcomes. No multicollinearity was detected, and all relevant interactions were considered. Additionally, the analysis of factors influencing discharge with a neurologically favorable outcome included targeted temperature management (TTM) as

a confounder. A P value of <0.05 was considered statistically significant.

2.7. Ethical Statement. This study was approved by the institutional review board at Hallym University (approval number: HDT 2019-06-004).

3. Results

The SALS database included 22,264 OHCA cases that occurred from January 2016 to December 2017. Of the 6,335 cases deemed eligible for the study, 4,154 (65.6%) occurred in a home. Furthermore, 52.2% of CA events in homes and 25.9% of events in public places occurred on a high floor (Figure 1). We found that OHCA events on a high floor in a home were more likely to involve a younger patient with a witness, shockable initial rhythm, and bystander CPR. OHCA events on a high floor in a public place were associated with an older age, nonshockable initial rhythm, and more frequent bystander CPR. The call-to-scene time was a median of 7 min, which is shorter on a high floor for events in both homes and public places. However, the call-to-patient time for home events was significantly longer on a high floor (a median of 9 min). Moreover, patients who experienced an OHCA event on a high floor at home were significantly more likely to experience a prehospital ROSC (25.39% vs. 21.22%), survival at admission (15.77% vs. 12.72%) and discharge (8.03% vs. 5.49%), and have favorable neurological outcome at discharge and have favorable neurological outcome at discharge (4.80% vs. 2.47%) after OHCA, compared to those who experienced OHCA on a low floor. In contrast, patients who experienced an OHCA event on a low floor in a public place were more likely to be alive on admission (22.94% vs. 16.31%), survive to discharge (15.27% vs. 8.88%), and have favorable neurological outcome at discharge (10.48% vs. 5.15%, Table 1).

Table 2 presents the aORs of clinical outcomes according to the arrest location after adjusting for sex, age, witness status, and bystander CPR. The prehospital ROSC, survival rate on admission, and survival rate at discharge after a high-floor OHCA event at home were positive, but not significant. In contrast, patients who experienced a high-floor OHCA in a public place had negative outcomes, with a significantly lower probability of survival discharge (aOR, 0.66; 95% CI, 0.47–0.92). In the multivariate analysis (Table 3), the likelihood of having favorable neurological outcomes at discharge after OHCA in a public place was significantly lower in the high-floor group (aOR, 0.58; 95% CI, 0.37–0.89), whereas at home, the probability of having favorable neurological outcomes at discharge was higher in the high-floor group (aOR, 1.40; 95% CI, 0.96–2.03). Male, younger age, witnessed arrest, bystander CPR, and TTM were associated with having favorable neurological outcomes at discharge regardless of CA location.

4. Discussion

Our results demonstrated that in a home setting, the floor height at which an OHCA event occurred did not affect the probability of a neurologically favorable outcome. In contrast, events that occurred on the lower floors of public places had a better prognosis than those that occurred on higher floors. Therefore, we cannot assume that the floor level in a high-rise building would necessarily impair the prognosis of an OHCA patient.

Early recognition and treatment access are key factors affecting patient survival after OHCA [5, 11]. Bystander CPR is considered the first step in both early recognition and access. Subsequently, a rapid EMS response time and resuscitation are considered significant predictors of patient survival after OHCA [12, 13]. Survival at discharge is also influenced by the allocation of EMS resources (e.g., ambulance density) [14]. The increasing urbanization of society and consequent increases in the numbers of users of high-rise buildings [15, 16] have led to concerns about delayed EMS responses due to issues of vertical access [8, 17, 18]. In South Korea, for example, apartment complexes comprising tower blocks have become increasingly common. In Seoul, approximately 80% of the population resides in apartment complexes, and these buildings account for 98% of all recent residential construction. Accordingly, the present study reported that 52.2% of high-floor OHCA events occurred in a home setting, a much higher proportion than those reported in other urban study areas (Osaka, 37.4%; Toronto, 22.4%) [8, 19]. However, it is doubtful whether an increase in vertical access time would increase the overall EMS response time or affect a patient's prognosis.

Patients who experience CA events on high floors are more likely than those on lower floors to be accessed and transported via elevators, which may be more advantageous than stairs. Additionally, skyscrapers tend to be located in city centers and are easily identifiable even if the building address has not been clearly stated. Moreover, in such cases, the ambulance will likely be required to travel a short distance to reach the building. Consistent with these factors, Conway et al. reported short call-to-scene times for incidents occurring in tall and large-volume buildings [20]. In this study, the call-to-scene times were shorter for events on high-levels in both public place and home settings. However, we found that the call-to-patient time varied in terms of the location of CA, with longer durations observed for low floors in home settings and high floors in public places. Consistent with a previous study, we found that a lack of access to an elevator that is sufficiently large to accommodate a stretcher, a lack of directional signage, and an entry code requirement are likely barriers to patient access in high-floor OHCA events at home [7]. Unlike previous studies, however, we observed shorter call-to-patient times in public places [7, 17, 19], which may be attributed to more accurate address reporting, open access ramps, and large elevators.

The demographic factors affecting a neurologically favorable discharge after OHCA varied greatly, depending on the floor height where the event occurred. OHCA events on higher floors at home tended to involve younger patients and were more frequently witnessed. Accordingly, the crude OR of a neurologically favorable discharge following OHCA at home was 1.94 times greater on a high floor than on a low floor. This finding was in contrast to previous studies [8, 18].

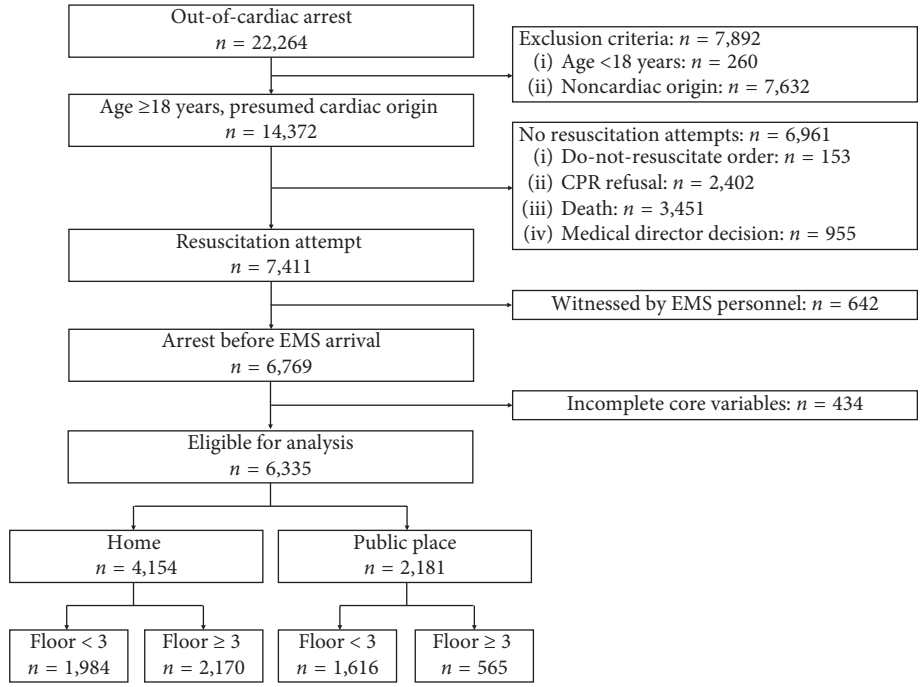

Figure 1: Overview of out-of-hospital cardiac arrest in home and public settings. CPR, cardiopulmonary resuscitation; EMS, emergency medical service.

Table 1: Demographic characteristics of out-of-hospital cardiac arrest patients according to the floor and location event.

	Home			Public place		
	<3rd floor	≥3rd floor	*P* value	<3rd floor	≥3rd floor	*P* value
Sex, male	1,214 (61.19)	1,357 (62.53)	0.388	1,208 (74.75)	314 (55.58)	<0.001
Age (years)	73.0 (60.0–80.0)	71.0 (56.0–80.0)	0.001	67.0 (54.0–79.0)	77.0 (61.8–84.0)	<0.001
Initial rhythm, shockable	245 (12.37)	322 (14.86)	0.021	522 (32.46)	93 (16.55)	<0.001
Witnessed	906 (46.11)	1,076 (50.00)	0.014	887 (55.86)	320 (57.04)	0.656
Bystander CPR	1,221 (61.82)	1,413 (65.39)	0.018	1,113 (69.48)	428 (76.29)	0.002
Call-to-scene time	8.0 (6.0–10.0)	7.0 (5.0–9.0)	<0.001	8.0 (6.0–11.0)	7.0 (5.0–8.0)	<0.001
Call-to-patient time	9.0 (7.0–12.0)	9.0 (8.0–12.0)	0.026	9.0 (7.0–12.0)	9.0 (7.0–12.0)	0.698
Outcomes						
Prehospital ROSC	421 (21.22)	551 (25.39)	0.002	518 (32.05)	158 (27.96)	0.073
Survival admission	252 (12.72)	341 (15.77)	0.005	370 (22.94)	92 (16.31)	0.001
Survival discharge	109 (5.49)	174 (8.03)	0.001	246 (15.27)	50 (8.88)	<0.001
Neurological favorable discharge	49 (2.47)	104 (4.80)	<0.001	169 (10.48)	29 (5.15)	<0.001

CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation.

In Korea, a higher income level is associated with living in a high-rise apartment [21]. We therefore presume that residents of a high-rising building have a high level of economic health.

We observed more striking differences in the characteristics of patients who experienced OHCA in a public place according to the floor where the event occurred. Events on low floors were significantly more likely to involve younger men with an initial shockable rhythm, and therefore the crude OR of a neurologically favorable discharge was high (2.03). This result is attributed to the locations of adult daycare centers in Korea. These centers are frequently located on the upper floors of commercial buildings in urban areas, as they are convenient for caregivers and in proximity to private hospitals or clinics. Accordingly, patients who experienced OHCA events on higher floors of public places were older and had a bystander CPR rate 76.3% higher than the overall rate. Moreover, although the access times did not differ between the high and low floors, the high-floor group had aORs for a neurologically favorably discharge as low as 0.58. This result suggests that our analysis did not correct for the patients' health statuses and comorbidities prior to the CA, as the users of adult daycare centers would be more likely to have existing diseases and disabilities.

This study had several limitations in addition to the above-mentioned failure to control for the patients' pre-CA health statuses. Most notably, this was a retrospective study of registry data, and therefore we could not determine the reasons for delayed patient access or the structural features of the locations of CA events.

Table 2: Adjusted odds ratios of clinical outcomes after a high-floor out-of-hospital cardiac arrest according to the event location.

Outcomes	Home	Public place
Prehospital ROSC	1.16 (0.99–1.35)	0.97 (0.77–1.21)
Survival admission	1.14 (0.94–1.37)	0.78 (0.59–1.01)
Survival discharge	1.24 (0.95–1.61)	0.66 (0.47–0.92)
Neurological favorable discharge	1.49 (1.04–2.15)	0.58 (0.38–0.90)

*Adjusted for sex, age, presence of witnesses, and bystander cardiopulmonary resuscitation.

Table 3: Associations of various factors with a neurologically favorable discharge according to the cardiac arrest location.

Outcome	Home	Public place
Sex, male	2.11 (1.36–3.28)	2.15 (1.36–3.40)
Age (year)	0.94 (0.93–0.95)	0.95 (0.94–0.96)
Witnessed	4.70 (3.04–7.25)	5.26 (3.44–8.05)
Bystander CPR	2.08 (1.33–3.24)	2.08 (1.33–3.24)
TTM	7.23 (4.59–11.39)	4.28 (2.48–7.41)
$\geq 3^{rd}$ floor	1.40 (0.96–2.03)	0.58 (0.37–0.89)

CPR, cardiopulmonary resuscitation; TTM, targeted temperature management.

Additionally, other confounding factors such as the quality of bystander CPR and automated external defibrillator use by bystanders may have influenced the association between the floor of patient contact and a neurologically favorable outcome after OHCA. However, we attempted to overcome these data limitations by combining EMS records with validated records of hospital treatments and outcomes.

5. Conclusion

We conclude that the nature of the setting (home vs. public place) affects the EMS response times to OHCA events in high-rise buildings, as well as the probability that a patient will achieve a neurologically favorable discharge following an event on a high floor. In other words, the patient's prognosis is more likely to be affected by the structure and use of the building, rather than by the floor height where the CA event occurred.

Data Availability

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

Conflicts of Interest

The authors report no conflicts of interest.

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Research Article

Three-Dimensional Shapes and Cell Deformability of Rat Red Blood Cells during and after Asphyxial Cardiac Arrest

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Changes in microcirculation are believed to perform an important role after cardiac arrest. In particular, rheological changes in red blood cells (RBCs) have been observed during and after ischemic-reperfusion injury. Employing three-dimensional laser interferometric microscopy, we investigated three-dimensional shapes and deformability of RBCs during and after asphyxial cardiac arrest in rats at the individual cell level. Rat cardiac arrest was induced by asphyxia. Five rats were maintained for 7 min of no-flow time, and then, cardiopulmonary resuscitation (CPR) was started. Blood samples were obtained before cardiac arrest, during CPR, and 60 min after return of spontaneous circulation (ROSC). Quantitative phase imaging (QPI) techniques based on laser interferometry were used to measure the three-dimensional refractive index (RI) tomograms of the RBC, from which structural and biochemical properties were retrieved. Dynamic membrane fluctuations in the cell membrane were also quantitatively and sensitively measured in order to investigate cell deformability. Mean corpuscular hemoglobin, mean cell volume, mean corpuscular hemoglobin concentration, and red blood cell distribution width remained unchanged during CPR and after ROSC compared with those before cardiac arrest. QPI results revealed that RBC membrane fluctuations, sphericity, and surface area did not change significantly during CPR or after ROSC compared with initial values. In conclusion, no three-dimensional shapes and cell deformability changes in RBCs were detected.

1. Introduction

Sudden cardiac arrest is one of the main causes of death worldwide. For decades, various research efforts have improved the survival of OHCA victims. However, the long-term neurologic prognosis of cardiac arrest victims still remains poor [1, 2].

Global I/R injury has important roles in a neurological injury of cardiac arrest victims. Cardiac arrest causes deprivation of blood supply to critical organs such as a brain, kidney, and myocardium. Energy stores in the brain are depleted entirely within the first few minutes of the acute ischemic period after cardiac arrest. Resuscitation and ROSC are essential for preventing the progression of irreversible tissue injuries. However, reperfusion of ischemic tissues results in both a local and a systemic inflammatory response and results in widespread microvascular dysfunction. These I/R injury and subsequent inflammatory responses are called postcardiac arrest syndrome. Although optimizing post-cardiac arrest care is emphasized and considered as the missing link of resuscitation, the exact mechanism of postcardiac arrest syndrome is not yet fully established [1–5].

Several recent studies have reported an essential role of RBCs in the modulation of the microcirculatory dysfunctions [6–13]. Previous experimental and clinical studies showed changes in morphology and rheological behavior of RBCs in various clinical conditions of I/R injury in sepsis,

severe trauma, and critically ill patients [6–16]. These changes contribute the microcirculatory dysfunction and the progress of the tissue injury [11, 17]. Microcirculatory dysfunction is also reported, and impaired microcirculation is related to poor prognosis in postcardiac arrest patients [18, 19].

The exact pathophysiology of microcirculation dysfunction of I-R injury is uncertain. Rheological changes in RBC are regarded as one of the critical factors of microcirculatory failure [7, 11–13, 17]. Cardiac arrest survivors also suffer from global IR injury, and microcirculatory changes also have important roles in the pathologic process of cardiac arrest survivors. Morphology and behavior changes of the RBCs can be present and expected to affect the progress of postcardiac arrest syndrome. However, few things are known about RBCs of postcardiac arrest, and no study has investigated changes in RBC rheology.

Here, we conducted experiments to determine whether rheological changes occur in rat RBCs during and after asphyxial cardiac arrest. In order to precisely and rapidly investigate individual cells, we employed a 3D quantitative phase imaging (QPI) technique and performed the measurements of the 3D shapes and cell deformability of individual RBCs during and after cardiac arrest. Based on the principle of laser interferometry, 3D refractive index (RI) tomograms, cytoplasmic Hb concentration, and dynamic membrane fluctuations of individual RBCs were retrieved. In particular, rheological properties of RBCs were also addressed by analyzing dynamic membrane fluctuations in a cell membrane. With this experiment, we wanted to evaluate the membrane properties, structures, and functional status of RBCs after cardiac arrest.

2. Materials and Methods

2.1. Animal Preparation. All animal studies were approved by the Institutional Animal Care and Use Committee of SMG-SNU Boramae Medical Center (IACUC no. 2014-0012) and the internal review board of KAIST (IRB Project no. 2012-0128). Five male Sprague Dawley rats (weight, 350–400 g) purchased at Koatech (Pyeongtaek, Korea) were used for experiments. The animals were housed under controlled laboratory conditions ($22 \pm 2^{\circ}$C; relative humidity, 55–60%), with free access to food and water before the experiment. The rats underwent an acclimatization period of 14 days before using in experiments.

2.2. Induction of Cardiac Arrest and Resuscitation Procedures. The animals were anesthetized with an intramuscular injection of zolazepam and tiletamine (Zoletil; Virbac AH, Fort Worth, TX, USA) and maintained on isoflurane (Choongwae Pharm, Seoul, Korea). Endotracheal intubation was done using a 16-gauge catheter (BD Instyle™ Autoguard™; Becton-Dickinson, Parsippany, NJ, USA) and assisted with a mechanical ventilator (tidal volume, 2 mL; respiratory rate, 60/min; FiO_2, 0.21; Harvard rodent ventilator model 557058, Harvard Apparatus, Holliston, MA, USA). The right femoral artery was cannulated to monitor blood pressure continuously and to sample blood. A tail vein was cannulated for drug administration. The ECG was recorded with the aid of subcutaneous patches. The ECG and femoral arterial blood pressure were recorded continuously on a monitor (DASH 4000, General Electric HealthCare Products, Arlington Heights, IL, USA) for subsequent analyses. Core temperature was measured with a rectal probe and controlled at $36.5 \pm 1.0^{\circ}$C using a warmer. Then, isoflurane inhalation was discontinued, and the animals were stabilized for 10 min.

As depicted in Figure1, asphyxia was induced by suspending ventilation for 10 min, and measurement of baseline parameters was begun by administering vecuronium (Reyon Pharm, Seoul, Republic of Korea) (0.05 mg/kg), stopping the ventilator, and kinking the ventilator connecting tube. Cardiac arrest was defined as MAP <20 mmHg and was maintained for 7 min. Then, CPR was started. The animals received intravenous epinephrine (0.005 mg/kg) prior to CPR. CPR included mechanical ventilation with 100% O_2 and 200 external manual chest compressions/min. ROSC was defined as a pulsatile MAP >50 mmHg. After ROSC, postresuscitation care was performed by administering sodium bicarbonate (1.0 mEq/kg) and changing the mechanical ventilator setting to achieve a respiratory rate of 60–70/min and to maintain the normocapnia according to our previous pilot study. Temperature control was stopped during CPR and restarted after ROSC.

2.3. Blood Sampling and Analyses. Three blood samples were obtained before cardiac arrest, during CPR (at 30 sec after initiation of CPR), and 60 min after ROSC (Figure 1). A total of 1.5 ml of blood was obtained each time and divided into one heparin-coated syringe and two tubes. The syringe (0.5 mL) was used to determine blood gases immediately after blood sampling using RAPIDPoint 405 (Siemens Healthcare, Erlangen, Germany), the one tube (0.5 mL) was used to check the CBC, and the other was used to check RBC rheology. The same volume of saline was infused after each blood sample was obtained. The first tube was sent to an external laboratory (Green Cross Laboratories, Gyeonggi-do, Korea) for CBC. The second tube was sent to the KAIST for the RBC rheological analysis.

2.4. Measurements and Outcome. We recorded the critical times during the experiment in the asphyxial cardiac arrest rat model, including the induction time of cardiac arrest and CPR time. All the blood samples were analyzed for CBC and blood gases, including MCV, MCH, MCHC, RDW, pH, PCO_2, PO_2, and HCO_3. Rat RBCs were collected in vacutainer tubes containing ethylenediaminetetraacetic acid to prevent blood clotting and quickly transported safely to the KAIST. We sent another blood sample with the study samples to determine any changes in the RBCs due to transport. The rat RBCs were centrifuged immediately upon arrival at KAIST at $2000 \times g$ at 10°C for 10 min to separate the RBCs from the plasma. The RBCs were washed three times with PBS.

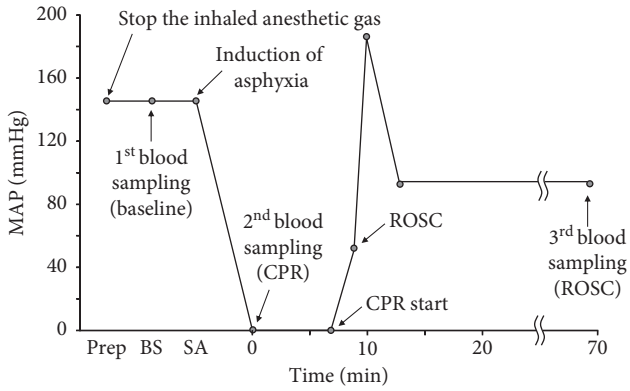

Figure 1: The change of mean arterial pressure in the asphyxial cardiac arrest model and time of blood sampling. MAP: mean arterial pressure; Prep: preparation; BA: baseline sampling; SA: start of asphyxia; ROSC: return of spontaneous circulation.

All blood samples sent to KAIST were analyzed for CHC, CM, CV, membrane fluctuations, surface area, and sphericity using cDOT. All the parameters are measured within 10 hours after collections of samples [20].

2.5. Common-Path Diffraction Optical Tomography (cDOT). We used common-path diffraction optical tomography (cDOT) to quantitatively and noninvasively measure the undulatory dynamics of the RBC membranes [21, 22]. Based on the principle of common-path laser interferometry and optical diffraction tomography, cDOT reconstructs the 3D RI tomogram of individual cells without labeling or other preparation processes. This label-free imaging capability makes the present method well suited for the application in emergency medicine. The 3D RI tomogram of a sample is reconstructed from multiple 2D phase distribution of the sample obtained with various illumination angles. This reconstruction process is done by solving an inverse problem of light propagations, also known as Helmholtz differential equation [23, 24]. This principle of optical diffraction tomography is an optical analog to X-ray computed tomography (CT) [25]. X-ray CT reconstructs the 3D absorptivity map of a human body, from multiple 2D projection images obtained with various illumination angles. In contrast, optical diffraction tomography reconstructs the 3D (RI) map of a cell, from multiple 2D projection images with various illumination angles. Because cDOT realizes the principle of optical diffraction tomography in common-path laser interferometry, cDOT provides the capability of highly sensitive measurements for 3D RI tomography [26, 27]. cDOT has shown potentials for the study of RBCs, including correlative analysis [21] and babesiosis [28].

A diode-pumped solid-state laser ($\lambda = 532$ nm, 50 mW, Cobolt Co., Solna, Sweden) was used as an illumination source for an inverted microscope. The microscope was equipped with a 60x oil immersion objective lens (1.42 NA) that facilitates diffraction-limited transverse resolution of about 200 nm. The overall magnification of the system was approximately 250x with the additional relay optics used outside the microscope. An sCMOS camera (Neo sCMOS, ANDOR Inc., Northern Ireland, U.K.) was used to image the interferograms. Employing common-path laser interferometry, cDOT provides highly stable full-field quantitative phase images of RBCs. The optical path-length stability was 2.4 mrad, which corresponds to membrane displacement of 3.3 nm. The details on the optical instrumentation and 3D reconstruction algorithms can be found elsewhere [29–31].

2.6. Analyses of the Red Cell Indices. Morphological (volume, surface area, and sphericity), biochemical (Hb concentration and content), and mechanical (dynamic membrane fluctuation) properties were retrieved from the measured 3D RI maps and 2D dynamic optical phase delay images.

To measure the morphological parameters, we used the 3D RI maps of individual RBCs measured using cDOT, $n(x, y, z)$. The cell volume was calculated by integrating all voxels inside individual RBCs. The size of each voxel (approx. $50\,\text{nm} \times 50\,\text{nm} \times 50\,\text{nm}$) was significantly smaller than the diffraction-limited size. The volume corresponding to the RBC cytoplasm was selected by RI higher than the threshold ($n_{\text{thresh}} = 1.363$). The total number of voxels was then counted to obtain the cell volume, considering the lateral magnification of the optical system. Next, the surface area of the RBC membrane was retrieved from the isosurfaces of individual RBCs. The surface area of the isosurface is measured through the summation of the areas of all the patch faces, which are broken down into small triangular pieces. In addition, the sphericity SI, a dimensionless quantity ranging from 0 to 1, was obtained by calculating $\text{SI} = \pi^{1/3}(6V)^{2/3}/A$, where the V is the volume and A is the surface area. A sphericity of 1 is close to a perfect sphere, and 0 is flat.

The Hb concentration of individual RBCs was calculated from the measured 3D RI maps of RBC cytoplasm. The Hb concentration is linearly proportional to the RI contrast, Δn, between an RBC and a surrounding medium as, $[\text{Hb}] = \alpha \cdot \Delta n$, where α is a refraction increment for Hb (0.2 mL/g) [32–34]. The Hb content in individual RBCs was then obtained by multiplying the cell volume by the Hb concentration.

From a set of the measured 2D optical phase delay images of each RBC $\Delta\phi(x, y, t)$ by cDOT, the dynamic cell height maps $h(x, y; t)$ were retrieved using the RI contrast $\Delta n = \langle n_{\text{RBC}} \rangle - n_{\text{medium}}$ between the RBC cytoplasm $\langle n_{\text{RBC}} \rangle$ and surrounding medium n_{medium}, as $h(x, y; t) = [\lambda/(2\pi \cdot \langle \Delta n \rangle)] \cdot \Delta\phi(x, y; t)$. Then, the representative 2D height profile of the corresponding RBC $\langle h(x, y; t) \rangle_t$ was obtained by taking a time average of the dynamic cell height maps. To quantitatively address the mechanical deformability of the membrane of individual RBCs during CPR and ROSC, the RMS of cell height displacement was calculated at each point on the cell and then averaged over the cell area, as $\Delta h = \langle [h(x, y; t) - \langle h(x, y) \rangle^2] \rangle^{1/2}$, where $\langle \cdot \rangle$ denotes a spatiotemporal average.

2.7. Statistical Analysis. The normality of the data distributions was assessed with the Kolmogorov–Smirnov test. Normally distributed, continuous data are expressed as mean ± standard deviation. Nonnormally distributed data

are expressed as median (interquartile ranges). Student's t-test was used to compare normally distributed data. A P value <0.05 was considered statistically significant. The Kruskal–Wallis test with the Mann–Whitney U post hoc test and Bonferroni correction were used for nonnormally distributed data among three groups, and a P value <0.017 was considered statistically significant. All analyses were performed using IBM SPSS 20 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Comparison of the Value of CBC and Arterial Blood Gas after Cardiac Arrest. To investigate the alterations in RBCs, we measured CBC values for rats undergo cardiac arrest induced by asphyxia. All rats were maintained for 7 min of no-flow time after mean arterial pressure was <20 mmHg, and then CPR was started. We performed postcardiac arrest care of rats after ROSC. Blood samples were obtained before cardiac arrest, during CPR, and 60 min after ROSC to check arterial blood gases and CBC.

Our result shows that the CBC values, including MCV, MCH, and MCHC, were not statistically different before cardiac arrest, during CPR, and 60 min after ROSC (Table 1). pH decreased during CPR (7.05 (7.00–7.11)) and was restored after ROSC (7.21 (7.12–7.28)) compared with that at baseline (7.32 (7.19–7.36)). PCO_2 increased during CPR (68.9 (59.8–77.2) mmHg) compared with that at baseline (39.0 (33.5–42.2) mmHg). PO_2 decreased during CPR (52 [35–47] mmHg)and was restored after ROSC (155 (96-170) mmHg). HCO_3 did not change significantly (P value = 0.859). The mean induction time to cardiac arrest was 2.0 ± 0.5 min, and the mean CPR duration was 2.0 ± 1.0 min. Mean rat rectal temperature before the cardiac arrest was $36.4 \pm 0.3^{\circ}$C and was $36.5 \pm 1.1^{\circ}$C after ROSC.

3.2. Morphological and Biochemical Alterations in Individual RBCs. To investigate structural alterations after CPR and ROSC at the individual cell levels, we measured 3D RI tomograms of RBCs, $n(x, y, z)$, using cDOT. For visualization purpose, the three cross-sectional slices (x-y, x-z, and y-z planes) of the reconstructed RI tomogram and the corresponding RI isosurface of the representative RBC in each RBC group are shown in Figure 2. In detail, for example, the 2D x-y cross-sectional slice of the RBC corresponds to $n(x, y, z = z_0)$, where z_0 is a manually determined z-coordinate of the RBC center plane. Then, from the 3D RI tomogram of individual RBCs, important red cell indices including Hb concentration, Hb content, and cell volume are retrieved, as shown in Figure 3 (for more detailed information, see *Materials and Methods*). The number of quantitatively measured and analyzed RBC in accordance with the sample time was 197 before cardiac arrest, 196 during CPR, and 197 after ROSC.

The Hb concentrations of RBCs in each group are shown in Figure 3(a). Hb concentration of individual RBCs was obtained from the tomographic measurements of RI values of RBC cytoplasm because RI contrast, Δn, between an RBC and a surrounding media is linearly proportional to Hb protein in RBC cytoplasm [21, 28, 48, 58].

Conducted statistical analyses did not guarantee any alteration in Hb concentration of measured RBCs of rats in both CPR and ROSC periods (Figure 3(a)). The mean values of the Hb concentration are 29.6 ± 2.1, 29.3 ± 2.0, and 29.5 ± 2.2 g/dL for RBCs in the baseline, CPR, and ROSC groups, respectively. This result is consistent with the CBC test (Table 1).

The Hb content or cellular dry mass of RBCs, i.e., the nonaqueous materials inside RBC, was obtained using the cDOT measurements [34]. The Hb content of RBCs does not exhibit significant changes during CPR and ROSC (Figure 3(b)). The mean values of the Hb content are 19.8 ± 3.0, 19.8 ± 3.1, and 20.0 ± 3.1 pg for RBCs in the baseline, CPR, and ROSC groups, respectively.

In addition, the cell volume does not exhibit statistical changes during CPR and ROSC, neither (Figure 3(c)). The cell volume was obtained by integrating voxels corresponding to cells in the measured 3D RI tomograms. The mean values of the cell volume are 66.7 ± 7.7, 67.2 ± 7.6, and 67.5 ± 7.7 fL for RBCs in the baseline, CPR, and ROSC groups, respectively. This result of the measurements of Hb content and cell volume agrees well with the CBC test (Table 1).

3.3. Deformability of Individual RBCs during CPR and ROSC. In order to investigate the rheological changes of individual RBCs during CPR and ROSC, the dynamic fluctuations in RBC membranes were quantitatively measured. Dynamic membrane fluctuations in RBCs, consisting of submicron displacements in the cell membrane, are strongly correlated with deformability and rheological properties of RBC [49, 50]. Previously, dynamic membrane fluctuations in RBC have been investigated for the study of alteration in rheological properties, caused by morphology [51], ATP [52, 53], osmotic pressure [27], malaria infection [54, 55], stored blood [56], cord blood [56], and diabetes mellitus [20].

The RBC maps in the first row in Figure 4 depict the 2D height profiles of the three representative RBCs in the baseline, CPR, and ROSC groups, respectively. Then, in order to visualize the dynamic fluctuating motion of RBC membranes, the root-mean-square (RMS) height fluctuation maps of corresponding RBCs were obtained from the time series of 2D height profiles, as shown in the second row in Figure 4 (for details, see *Materials and Methods*).

The averaged RMS height fluctuations of individual RBCs during the baseline, CPR, and ROSC groups are shown in Figure 5(a). Experiments were conducted on five rats to address animal-to-animal variations. For each rat, a total of 120 RBCs were measured using cDOT. Although there exist variations between rats, the values of the RMS height fluctuation of RBCs do not exhibit significant alterations during CPR and ROSC, in comparison with those of the baseline group. The mean values of the averaged RMS height fluctuation are 49.1 ± 6.0, 50.3 ± 5.7, and 49.2 ± 4.9 nm for RBCs in the baseline, CPR, and ROSC groups, respectively. This result clearly indicates that the deformability of

Table 1: The comparison of the value of the CBC and arterial blood gas analysis according to the sample time.

	Baseline	During CPR	60 min after ROSC	P value
pH	7.32 (7.19–7.36)	7.05 (7.00–7.11)	7.21 (7.12–7.28)	0.011
PCO_2 (mmHg)	39.0 (33.5–42.2)	68.9 (59.8–77.2)	56.3 (40.2–84.7)	0.018
PO_2 (mmHg)	312 (240–361)	52 [35–47]	155 (96–170)	0.002
HCO_3 (mEq/L)	17.8 (15.1–20.1)	18.6 (16.6–20.8)	17.8 (16.4–19.4)	0.859
Hemoglobin (g/dL)	14.3 (14.0–14.6)	13.7 (11.5–14.2)	14.1 (13.0–14.7)	0.223
Hematocrit (%)	48 [36–39]	42 [35–37, 48–57]	47 [35–39, 57]	0.658
MCV (fL)	67.5 (67.7–69.4)	70.8 (70.1–71.6)	67.7 (65.5–69.0)	0.164
MCH (pg)	19.9 (19.8–20.0)	20.1 (19.5–20.2)	20.0 (19.9–20.1)	0.883
MCHC (g/dL)	29.6 (28.8–29.7)	28.5 (28.1–28.5)	29.6 (28.8–30.2)	0.183
RDW (%)	12.8 (12.3–15.6)	12.3 (11.4–12.5)	12.1 (11.8–12.2)	0.227
Body temperature (°C)	36.3 (36.3–36.4)	35.3 (34.5–36.0)	36.8 (36.4–37.0)	0.036

Values are expressed as median with interquartile range. CBC: complete blood count; CPR: cardiopulmonary resuscitation; ROSC: return of spontaneous circulation; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; RDW: red cell distribution width.

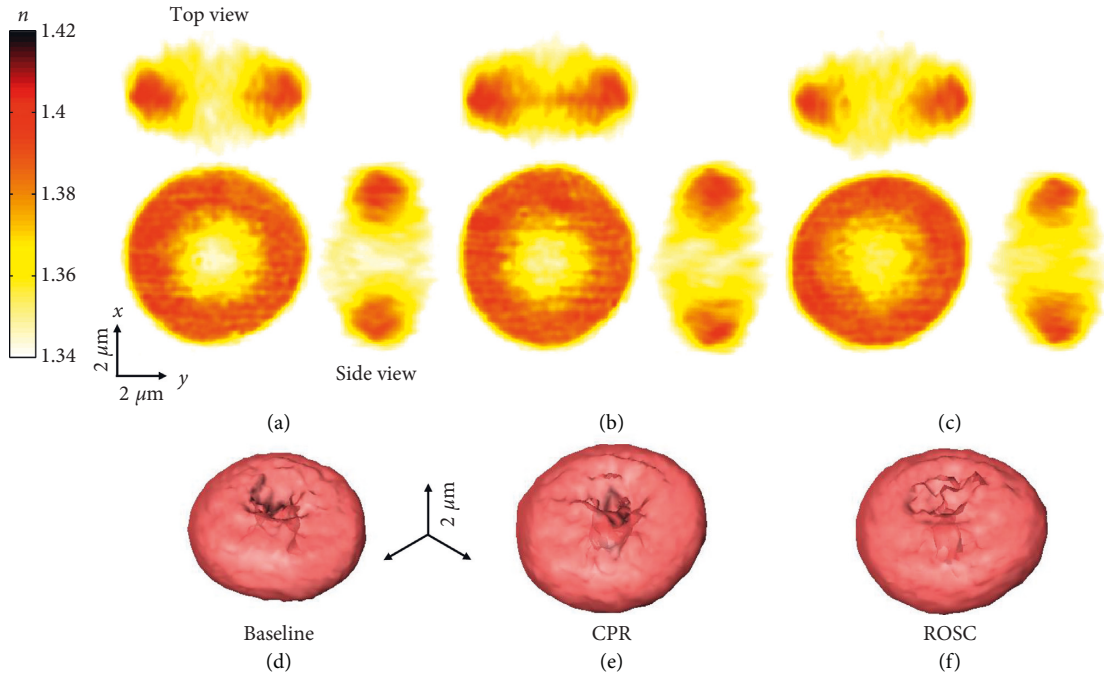

Figure 2: The reconstructed 3D RI distribution of RBCs. (a–c) Three 2D cross sections (x-y, x-z, and y-z planes) of the 3D RI map for the representative RBC from baseline, CPR, and ROSC groups, respectively. (d–f) 3D rendered RI isosurfaces of the corresponding three representative RBCs.

individual RBCs is not significantly changed during the CPR and ROSC.

To further analyze the alterations in morphologies of individual RBCs, the values of the surface area and sphericity were retrieved. The result is shown in Figure 5(b) and it is clearly seen that there is no statistical difference in the cell surface area between RBCs in the baseline, CPR, and ROSC groups. The mean values of the cell surface area are 115.9 ± 9.6, 115.5 ± 8.9, and $115.3 \pm 9.6\,\mu$m2 for RBCs in the baseline, CPR, and ROSC groups, respectively. These results exclude the possibility of significant microvesiculation during the CPR and ROSC.

From the measured cell volume and surface area, sphericity, a unit-less parameter indicating the roundness of a cell, was calculated. The result is shown in Figure 5(c). These results show that the overall roundness of individual cells is not significantly altered during CPR and ROSC. The result can also be expected from the observations that both the cell volume and surface area were not changed during CPR and ROSC.

4. Discussion

This study is, to our knowledge, the first study evaluating RBC rheology changes during or after cardiac arrest. No morphologic, biochemical, and deformability changes occurred in rat RBCs during and 60 min after asphyxial cardiac arrest compared with those at baseline. The rat RBCs remained unchanged throughout the experimental period. The duration of arrest time including induction is typically

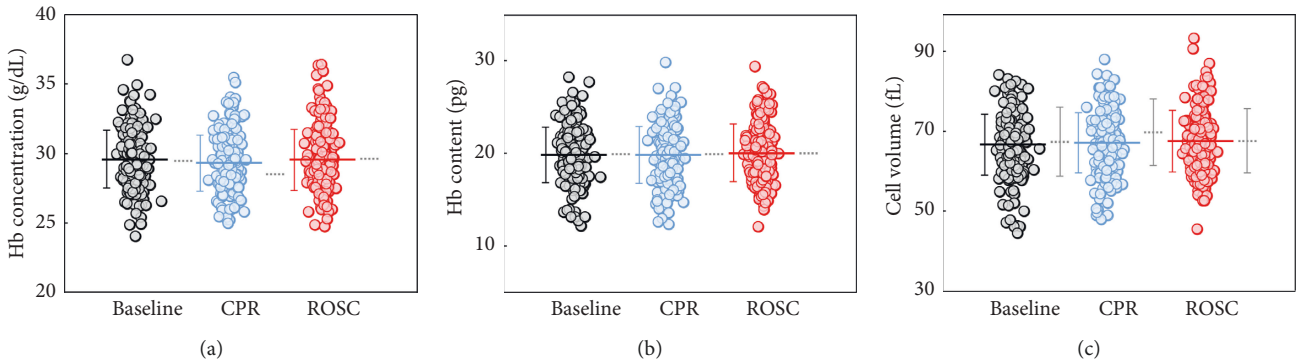

FIGURE 3: Red cell parameters of individual RBCs. (a) Hb concentration, (b) Hb content, and (c) cell volume of individual RBCs in groups of the baseline, CPR, and ROSC, respectively. ∗ indicates P value <0.05. Each symbol represents individual RBC measurements, and the horizontal lines are mean values with vertical lines of standard deviation error bars. Horizontal gray dotted lines in (a)–(c) correspond to mean cellular Hb concentration (MCHC), mean cellular Hb content (MCH), and mean cellular volume (MCV), respectively.

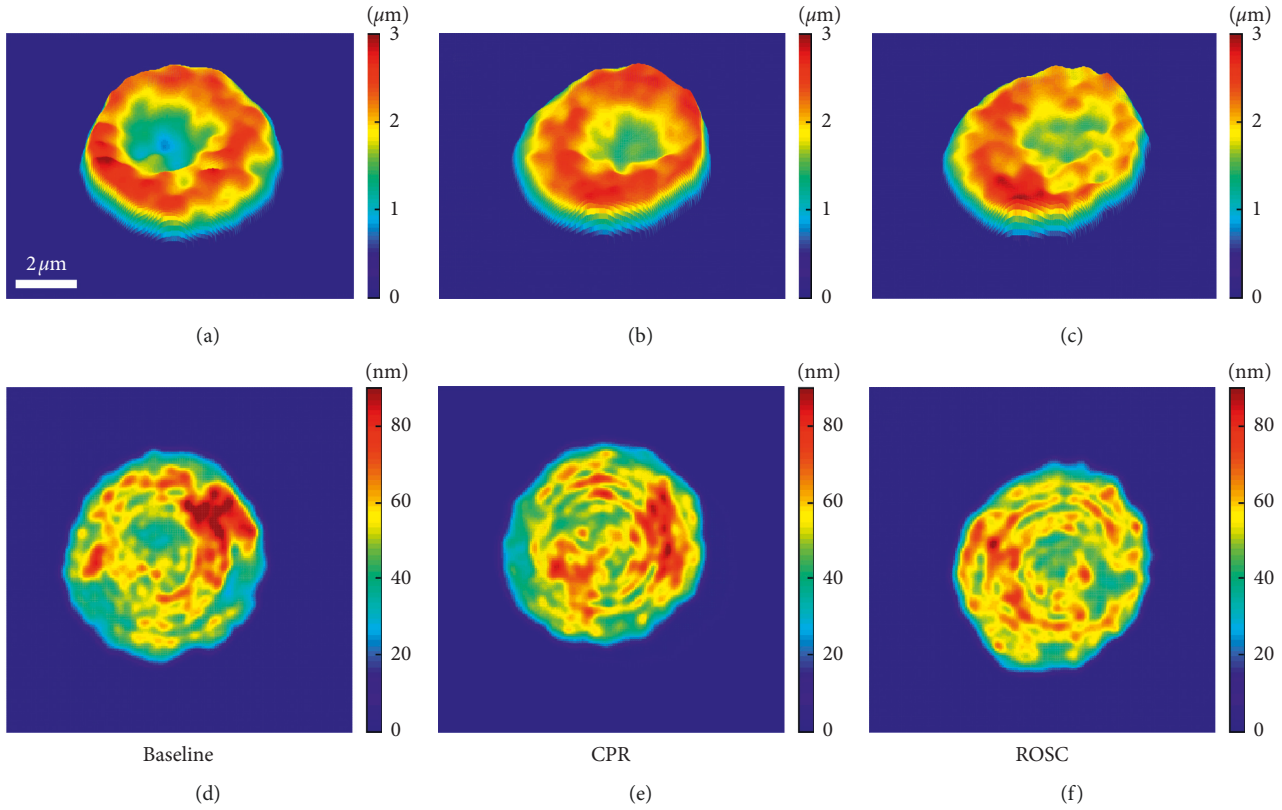

FIGURE 4: (a)–(c) 2D height profiles of the representative RBC from baseline, CPR, and ROSC groups, respectively. (d)–(f) 2D RMC fluctuation maps of the corresponding three representative RBCs.

<9 min in many experimental preclinical cardiac arrest animal models [35–41, 57]. Brain damage often occurs due to asphyxia after 7 min in the cardiac arrest rat model. Many studies have investigated the effects of various interventions using this model. The total mean asphyxia time with cardiac arrest was about 9 min in our study. No-flow time, which is true arrest time, was 7 min. Thus, 7 min of cardiac arrest was sufficient to cause systemic ischemia.

In one previous study, ischemia has been induced in rat hind limbs by occluding the femoral artery for 10 min, followed by reperfusion. RBC deformability as measured by ektacytometry was significantly impaired immediately after the ischemic period in blood samples obtained from the femoral vein of the ischemic limb, but no significant difference was observed after 15 min of reperfusion [10]. In another study, I/R was produced by clipping the superior mesenteric artery for 30 min, and the area was reperfused for 60 min before extermination. Blood samples were taken from the caudal caval vein and from the portal vein before ischemia, 1 min before and after clip removal, and after 15, 30, and 60 min of reperfusion. RBC deformability was determined by slit-flow ektacytometry based on the

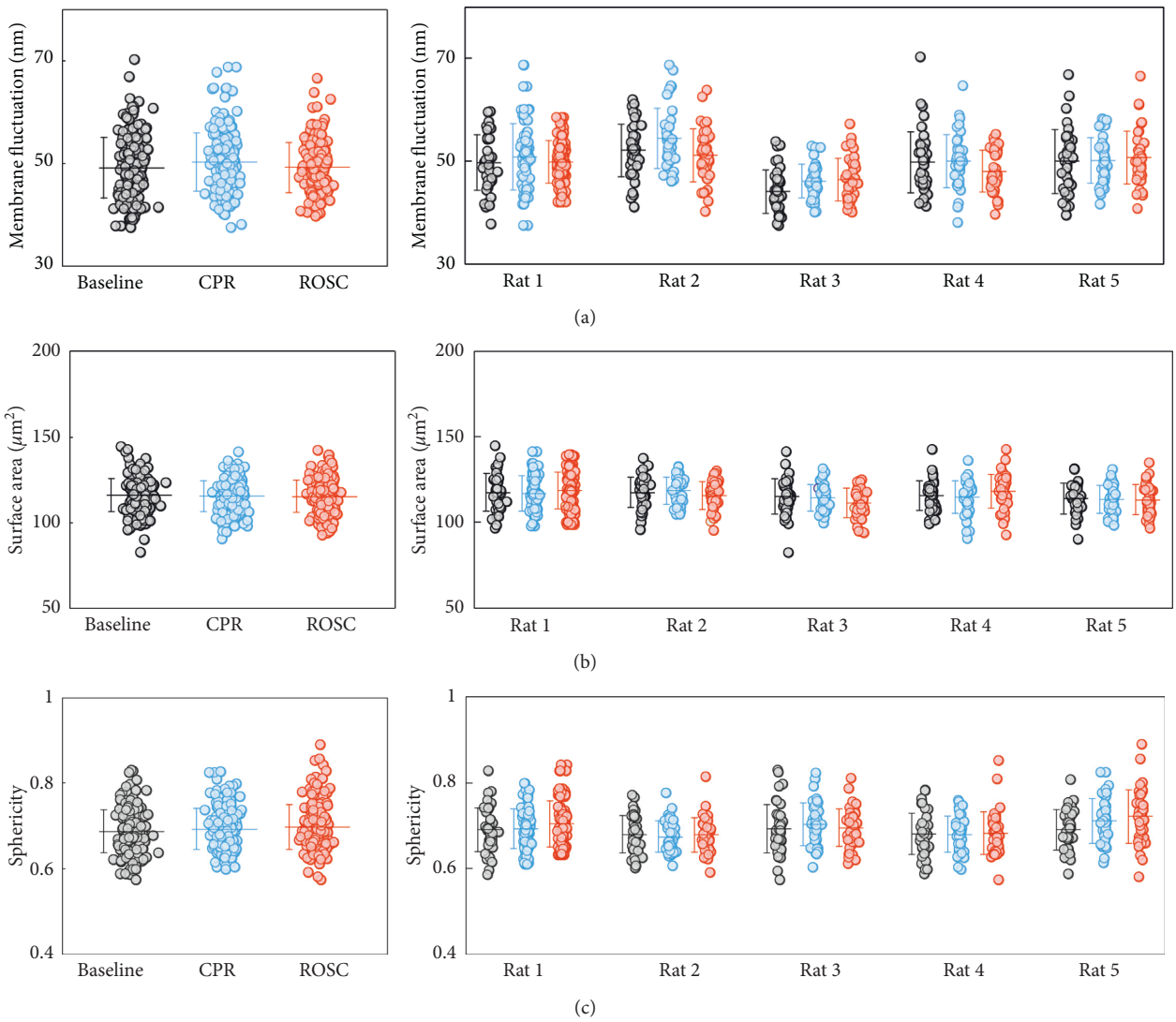

Figure 5: Dynamic membrane fluctuations, sphericity, and surface area of individual RBCs using CPR and ROSC. (a) RMC fluctuation of the cell membrane of individual RBCs, (b) cell surface area, and (c) sphericity. Each symbol represents individual RBC measurements, and the horizontal lines are mean values with vertical lines of standard deviation error bars.

erythrocyte laser diffraction image analysis at various levels of shear stress. RBC deformability worsened significantly in the I/R group during the experimental period compared to that at baseline and in the sham group [16].

Some studies have been performed on RBC rheology in critically ill patients or those with sepsis. A previous review article reported that changes in RBC rheology can contribute to microvascular injury and the impaired oxygen supply seen in patients with sepsis [8]. Many factors are involved in RBC rheology, including nitric oxide, reactive oxygen species, altered calcium homeostasis, decreases in ATP reserves, increases in intracellular 2,3 diphosphoglycerate, membrane components (sialic acid), and interactions with white blood cells. These findings suggest that understanding the mechanisms of the changes in RBC rheology in patients with sepsis and their effects on blood flow and oxygen transport may lead to improved patient management and reduced morbidity and mortality. In another study, a total of 196 patients in the ICU (160 without and 36 with sepsis) and 20 healthy volunteers were studied by laser-assisted optical rotational cell analysis within the first 24 hours after ICU admission for an RBC rheological assessment [12]. They showed that early changes in RBC rheology are common in patients in the ICU, particularly in those with sepsis. These changes may contribute to the microcirculatory alterations observed in critically ill patients. Two studies have been performed about changes in RBC rheology over time in critically ill patients with sepsis and their relationships with outcome or prognosis [25, 26]. They concluded that changes in RBC rheology and deformability are useful to estimate the prognosis of patients with sepsis and that reduced RBC deformability over time is associated with a poor outcome.

Early-stage microcirculatory dysfunction is also reported in cardiac arrest victims. Van Genderen et al. reported early microcirculatory dysfunction of postcardiac arrest patients, and it is caused by vasoconstriction due to induced systemic

hypothermia [42]. Omar et al. also reported microcirculatory dysfunction in the early stage and there was no statistical relationship between degrees of impairment of microcirculation and levels of cytokines and lactate [19]. Inflammatory responses are regarded as one of the most important factors which induce hemorheological changes of RBC [17]. Properties of RBC were not changed at 60 min after ROSC in our study. Early microcirculatory dysfunction of postcardiac arrest may not relate to inflammatory response and RBC rheology changes.

DPM is a QPI technique and has been widely used to investigate RBC deformability [27–29]. Dynamic membrane fluctuations, consisting of submicron displacement in the cell membrane, are strongly correlated with RBC deformability and rheological properties [30, 31]. Using DPM, several alterations in deformability of RBCs have been investigated, including the effects of ATP and the behavior of RBC deformability in response to various osmotic pressures.

The biomechanical properties of RBCs are crucial for their physiology. This essential deformability is, in turn, affected by various pathophysiological conditions. Temperature plays an important role in deformability of RBCs [43, 54]. Extracellular media of different osmolalities causes changes in RBC morphology and, thus, deformability [44]. The presence of ATP is essential for the RBC to maintain their biconcave shape and significantly affects RBC deformability [45, 51]. Malaria infection results in significant modifications to the rheological properties of host RBCs. Membrane fluctuation measurements show an increased shear modulus and a loss of deformability in malaria-infected RBCs [46, 54]. Quantitative phase microscopy has been used to measure a decrease in membrane fluctuations in sickled RBCs [47]. Diabetic RBCs showed diminished membrane fluctuation and reduced deformability [20].

Several limitations of our study should be mentioned. First, we used a nonhuman, small rodent, rat cardiac arrest model. Some differences may occur between rat RBCs and human RBCs during global ischemia, CPR, and after ROSC. Second, we did not have samples more than 60 minutes after ROSC because of time limitations to conduct the RBC analyses. However, as mentioned above in the limb ischemia model, RBC rheology changes were started earlier than 60 minutes. Further study is needed to analyze blood samples for an extended time period. Third, we did not evaluate RBCs of extended durations of arrest time. Fourth, we did not measure inflammatory cytokines and microvascular flow which can reflect the systemic inflammation and tissue perfusion status. Fifth, other parameters such as blood viscosity, shear rate, and plasma flow rate were not directly evaluated. Also, in vivo analysis of the rheological change was not evaluated.

5. Conclusion

Three-dimensional shapes and cell deformability changes of the RBCs were not observed in a 7 min cardiac arrest rat model of asphyxia, such as fluctuations, surface area, or sphericity, during CPR and 60 min after ROSC using cDOT. Additional research is needed to determine whether RBCs undergo rheological changes in patients suffering from cardiac arrest.

Data Availability

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

Disclosure

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

Conflicts of Interest

All authors declare no conflicts of interest.

Authors' Contributions

Jonghwan Shin, Hui Jai Lee, HyunJoo Park, and YongKeun Park developed the experimental idea. SangYun Lee, Hui Jai Lee, HyunJoo Park, and YongKeun Park performed the experiments and analyzed the data. Jonghwan Shin and Hui Jai Lee prepared blood samples. Jonghwan Shin and YongKeun Park supervised the study. All authors discussed the experimental results and wrote the manuscript. Hui Jai Lee and SangYun Lee contributed equally to this study.

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Research Article

Use High-Flow Nasal Cannula for Acute Respiratory Failure Patients in the Emergency Department: A Meta-Analysis Study

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Objective. To evaluate the efficacy of high-flow nasal cannula (HFNC) therapy compared with conventional oxygen therapy (COT) or noninvasive ventilation (NIV) for the treatment of acute respiratory failure (ARF) in emergency departments (EDs). *Method*. We comprehensively searched 3 databases (PubMed, EMBASE, and the Cochrane Library) for articles published from database inception to 12 July 2019. This study included only randomized controlled trials (RCTs) that were conducted in EDs and compared HFNC therapy with COT or NIV. The primary outcome was the intubation rate. The secondary outcomes were the mortality rate, intensive care unit (ICU) admission rate, ED discharge rate, need for escalation, length of ED stay, length of hospital stay, and patient dyspnea and comfort scores. *Result*. Five RCTs ($n = 775$) were included. There was a decreasing trend regarding the application of HFNC therapy and the intubation rate, but the difference was not statistically significant (RR, 0.53; 95% CI, 0.26–1.09; $p = 0.08$; $I^2 = 0\%$). We found that compared with patients who underwent COT, those who underwent HFNC therapy had a reduced need for escalation (RR, 0.41; 95% CI, 0.22–0.78; $p = 0.006$; $I^2 = 0\%$), reduced dyspnea scores (MD −0.82, 95% CI −1.45 to −0.18), and improved comfort (SMD −0.76 SD, 95% CI −1.01 to −0.51). Compared with the COT group, the HFNC therapy group had a similar mortality rate (RR, 1.25; 95% CI, 0.79–1.99; $p = 0.34$; $I^2 = 0\%$), ICU admission rate (RR, 1.11; 95% CI, 0.58–2.12; $p = 0.76$; $I^2 = 0\%$), ED discharge rate (RR, 1.04; 95% CI, 0.63–1.72; $p = 0.87$; $I^2 = 0\%$), length of ED stay (MD 1.66, 95% CI −0.95 to 4.27), and hospital stay (MD 0.9, 95% CI −2.06 to 3.87). *Conclusion*. Administering HFNC therapy in ARF patients in EDs might decrease the intubation rate compared with COT. In addition, it can decrease the need for escalation, decrease the patient's dyspnea level, and increase the patient's comfort level compared with COT.

1. Background

Acute respiratory failure (ARF) is a critical condition faced in emergency departments (EDs). It can result from many conditions, such as cardiogenic pulmonary edema, pneumonia, or acute exacerbation of chronic obstructive pulmonary disease and has a high mortality rate [1]. Conventional oxygen therapy (COT), including a nasal cannula, face mask, venturi mask, and nonrebreathing mask, can be provided to correct hypoxemia. However, the maximal flow rate of COT devices is 15 L/min, which is not enough for patients with ARF. Thus, escalating oxygen therapy to noninvasive ventilation (NIV, e.g., biphasic positive airway pressure) or invasive ventilation may be needed.

Some studies have demonstrated that intubation in ARF patients is associated with an increased complication rate and mortality rate when compared with NIV [2–4]. Even so, NIV is associated with some disadvantages, such as gastric distension, vomiting, claustrophobia, possible nasal skin damage, and difficulty in speaking and coughing, and may lead to treatment failure [5]. According to a previous report, the NIV failure rate in ARF patients ranges from 5% to 60%, depending on numerous factors [6]. Another investigation revealed that up to 25% of chronic obstructive pulmonary disease acute exacerbation patients do not tolerate NIV for several reasons [7]. Therefore, using an ideal NIV device for patients not only improves comfort and dyspnea levels but also decreases intubation and mortality rates potentially.

In recent years, many studies have shown clinical benefits associated with high-flow nasal cannula (HFNC) therapy in ARF patients [8], the oxygen support of preoxygenation [9], acute pulmonary edema [10], the maintenance of oxygenation during bronchoscopy [11], and the prevention of reintubation [12] because an HFNC can provide warmed, humidified, and up to 100% oxygen. When compared to COT and NIV, HFNC therapy has some potential advantages. First, an HFNC can deliver a constant and wide FiO_2 range according to the patient's needs. Second, a maximum flow of 60 L/min can generate positive end-expiratory pressure, resulting in the elimination of some airway dead space, improving oxygenation [13]. Third, inspired warm and humidified oxygen can optimize mucosal functions, maximize mucociliary clearance and help expectoration [14]. Finally, using an HFNC can decrease the interruption of oxygen therapy (e.g., during eating, drinking, or talking) and increase patient compliance, resulting in potentially improved outcomes [15]. Previous systematic reviews analyzing heterogeneous study methods (combining observational and randomized controlled trial (RCT) data [16]) and populations (combined ICU and ED populations [17]; those with ARF, and postextubation and postoperation populations [18, 19]) may cause controversial results. Thus, clarifying the use of HFNCs for ARF patients in EDs is necessary. In this study, we conducted a recent systematic review and meta-analysis to evaluate the differences between using HFNC therapy and COT or NIV in ARF patients in EDs.

2. Methods

This study design followed the Cochrane Handbook for Systematic Reviews of Interventions guidelines [20] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements [21].

3. Eligibility Criteria

3.1. Types of Studies. Only RCTs were eligible. We excluded retrospective studies, observational studies, before-after studies, crossover studies, case reports, abstract publications, and conference presentations.

3.2. Types of Participants. We included adult patients (>18 years old) with ARF due to any cause admitted to ED. "ARF" was defined as an SpO2 <92% in room air, a PaO_2/FiO_2 (ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen) <300, clinical symptoms and signs (including a respiratory rate >24 breaths per minute, the use of accessory muscles to breath, or shortness of breath at rest) or "author" definitions. Postoperation, postextubation, and ICU patients were all excluded.

3.3. Types of Interventions. Studies comparing HFNC therapy with COT and/or other NIV devices were included. There was no oxygen flow or concentration restriction for the intervention group (HFNC) or the comparison group (COT and/or other NIV devices).

3.4. Types of Outcome Measures. Our primary outcome was the intubation rates of both of the groups. The secondary outcomes were the mortality rate, ICU admission rate, ED discharge rate, need for escalation, length of ED stay, length of hospital stay, and patient dyspnea and comfort scores. We also considered 2 subgroup analyses according to the intervention device (HFNC versus COT and NIV versus COT) and treatment duration (HFNC ≤2 hours versus COT and HFNC >2 hours versus COT).

3.5. Search Methods for Identification of Studies. We comprehensively searched 3 databases (PubMed, EMBASE, and the Cochrane Library) for articles published from database inception to 12 July 2019. The following key words or medical subject headings (MeSH) terms were used: *high-flow nasal cannula*, *high-flow nasal*, *high-flow oxygen therapy*, or *high-flow therapy*, and *emergency department*, *emergency room*, *emergency unit*, *or emergency service*. To avoid the loss of possible studies, we also reviewed the references of the identified articles. No language restriction was applied.

3.6. Data Extraction, Quality Assessment, and Grading of the Quality of Evidence. Two authors (CCH and HML) extracted the data from the reviewed articles independently. We used an unweighted kappa score to test interrater reliability. If any disagreement occurred, it was resolved by discussion, consensus, or consultation with a third author

(CJL). The following data were collected for each eligible study: authors, publication year, study design, study group, intervention/control detail, and outcome data.

The risk of bias was independently assessed by two authors (CCH and HML) according to the Cochrane Handbook for Systematic Reviews of Interventions guidelines, chapter 8 [20]. There were 7 domains that were assessed for each study: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Each domain was rated as having low risk (green), unclear risk (yellow), or high risk (red).

We also used the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) method [22] to evaluate the quality of evidence, which was classified as very low, low, moderate, or high, for the primary and secondary outcomes.

3.7. Statistical Analysis. All data were analyzed by Review Manager (RevMan, Version 5.3, Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014). Because some of the included studies presented results as medians, interquartile ranges, or minimum/maximum values, we use the Wan et al. method to estimate the sample mean and standard deviation [23]. We expressed dichotomous data as risk ratios (RRs) and continuous data as mean differences (MDs) or standardized mean differences (SMDs). For all of the results, 95% confidence intervals (CIs) were calculated. To evaluate heterogeneity, we used chi-square and I^2 tests. If the heterogeneity was nonsignificant ($I^2 < 50\%$), we applied fixed-effects models; otherwise, we applied random-effects models for analysis. In addition, we performed a visual inspection of the funnel plot to assess publication bias, and a sensitivity analysis was conducted by repeating the analysis after removing one RCT at a time. Finally, the results were presented in forest plots.

4. Result

A total of 2371 potentially eligible studies were initially identified. After screening titles and abstracts, 55 full-text studies were retrieved for eligibility screening. Then, we excluded studies conducted in ICU settings, review articles, nonrandomized controlled trials, case reports, conference abstracts, studies involving non-ARF patients, and studies involving pediatric patients. Finally, 5 RCTs [24–28] including 775 patients were entered into our meta-analysis (Figure 1). The interrater reliability of study screening (kappa score, 0.76; 95% CI, 0.68–0.86) and risk of bias assessment (kappa statistic 0.77, 95% CI: 0.57–0.98) were good. The mean age ranged from 63.4 to 73.7 years old. Of the 5 RCTs, 1 RCT [28] compared HFNC therapy with NIV and the others [24–27] compared HFNC therapy with COT (nasal cannula, face mask, venturi mask, or nonrebreathing mask). The flow in the HFNC group was 35 L/min or more at initiation, and the duration of therapy ranged from 1 hour to 72 hours. The main causes of ARF were chronic obstructive pulmonary disease (COPD), pneumonia, and cardiac-related disease in our included studies. The basic characteristics of the included studies are shown in Table 1. Owing to the lack of an NIV group in the other studies, we were not able to analyze the RCT [28] that compared HFNC with NIV. In addition, there was no event (intubation) in one RCT [25], and the data in the included studies were too insufficient to obtain valuable conclusions. Because of the above 2 reasons, we were not able to perform subgroup analyses.

4.1. Risk of Bias of the Included Studies. The risk of selection bias in our included studies was all low, except for 1 RCT [25] that had an unclear risk of bias. The risk of performance bias was all high because it was impossible to blind patients and personnel in the clinical setting when comparing HFNC to COT. The other risk of bias results is shown in Figure 2.

4.2. Quality Assessment. Table 2 summarizes all outcomes and the quality of evidence of the articles included in this meta-analysis. The intubation rate, length of ED/hospital stay, and patient dyspnea level were of low quality, and the others were of moderate quality. A visual inspection of the funnel plot revealed no publication bias (Additional file 1).

4.3. Primary Outcome. Four RCTs including 571 patients reported the intubation rates for both groups. Ten of 296 (3.38%) patients in the HFNC group were intubated, and 17 of 275 (6.18%) patients in the COT group were intubated. There was a decreasing trend of HFNC therapy and intubation rate, but it was not statistically significant (RR, 0.53; 95% CI, 0.26–1.09; $p = 0.08$; $I^2 = 0\%$) (Figure 3(a)).

4.4. Secondary Outcomes

4.4.1. Mortality, ICU Admission Rate, and ED Discharge Rate. We did not observe a difference in the mortality rate (RR, 1.25; 95% CI, 0.79–1.99; $p = 0.34$; $I^2 = 0\%$), ICU admission rate (RR, 1.11; 95% CI, 0.58–2.12; $p = 0.76$; $I^2 = 0\%$), or ED discharge rate (RR, 1.04; 95% CI, 0.63–1.72; $p = 0.87$; $I^2 = 0\%$) between the HFNC and COT groups (Figures 3(b), 4(a), and 4(b)).

4.4.2. Need for Escalation. If the patient could not tolerate initial therapy (HFNC therapy or COT) or therapy failed, patient oxygenation required escalation to avoid hypoxia. The escalation strategies in our included studies were similar. Two RCTs [26, 27] escalated to NIV or invasive ventilation in both the HFNC and COT groups. One RCT [24] escalated to NIV or invasive ventilation in the HFNC group and HFNC, NIV or invasive ventilation in the COT group. No escalation was needed in 1 RCT [25]. HFNC therapy decreased the need for escalation compared to

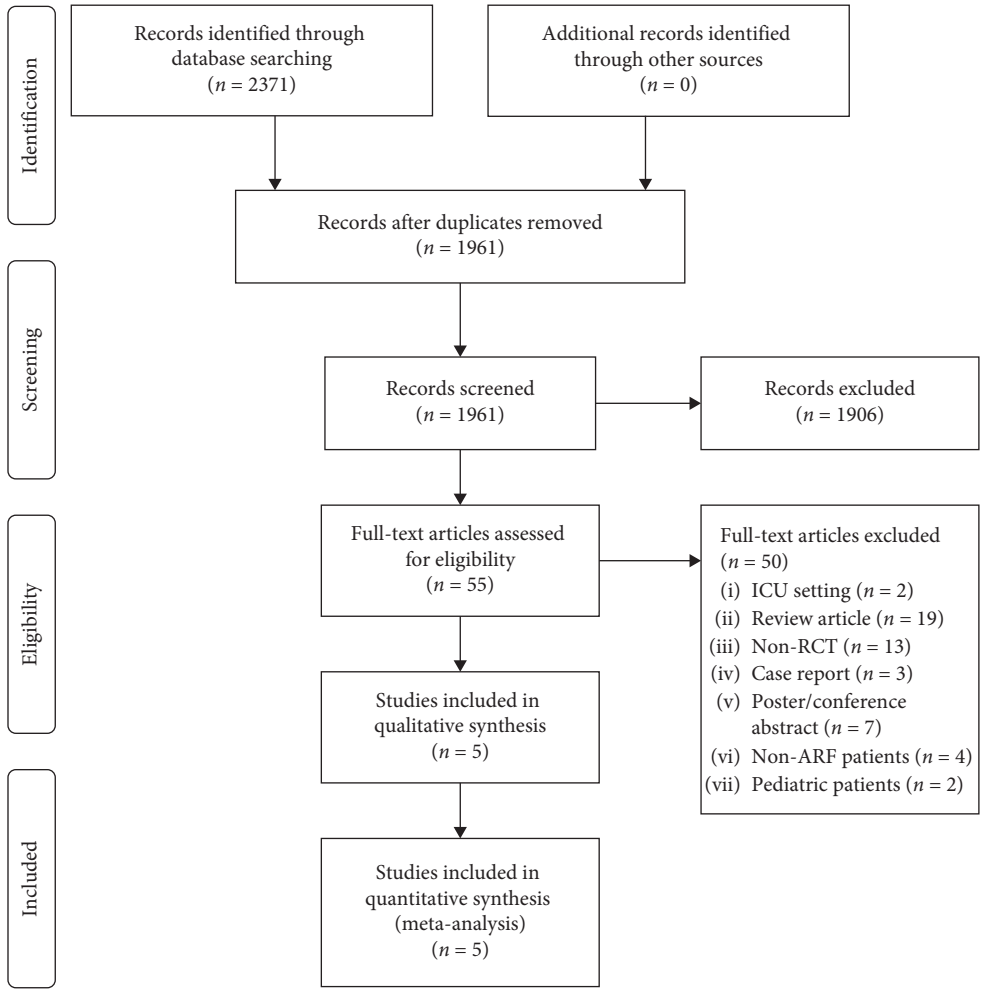


Figure 1: PRISMA flow diagram.

Table 1: The basic characteristics of the included studies.

Study, year	Design	Setting	Age, years*	Cause of ARF	Sample size			Duration of therapy
					HFNC	COT	NIV	
Bell et al. [24]	RCT	ED	73.7 ± 17.5	COPD, respiratory tract infection, cardiac related, pulmonary embolism, asthma	48	52	—	2 h
Rittayamai et al. [25]	RCT	ED	64.6 ± 15.1	CHF, pneumonia, asthma, COPD, others	20	20	—	1 h
Jones et al. [26]	RCT	ED	73.5 ± 16.2	COPD, pneumonia, asthma, others	165	138	—	5 h
Makdee et al. [27]	RCT	ED	70 ± 15	Cardiogenic pulmonary edema	63	65	—	2.9 h (0.2–9.3 h)
Doshi et al. [28]	RCT	ED	63.4 ± 14	COPD, CHF, pneumonia, asthma	104	—	100	72 h

RCT, randomized controlled trial; ED, emergency department; COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; h, hours. *Mean ± standard deviation (SD).

COT (RR, 0.41; 95% CI, 0.22–0.78; $p = 0.006$; $I^2 = 0\%$) (Figure 4(c)).

4.4.3. Length of ED Stay and Hospital Stay. The length of ED stay (MD 1.66, 95% CI −0.95 to 4.27) and hospital stay (MD 0.9, 95% CI −2.06 to 3.87) were similar in both the HFNC and COT groups (Table 2).

4.4.4. Dyspnea Score. The dyspnea score in the HFNC group was significantly lower than that in the COT group (MD −0.82, 95% CI −1.45 to −0.18) (Table 2). Two of the 4 RCTs reported measurable dyspnea scores. One RCT [25] used a numerical rating scale ranging from 0 to 10, and the other RCT [27] used a visual analog scale ranging from 0 to 10. Of the included RCTs, 1 RCT [24] defined patient dyspnea as a reduction in the respiratory rate >20% from baseline and a

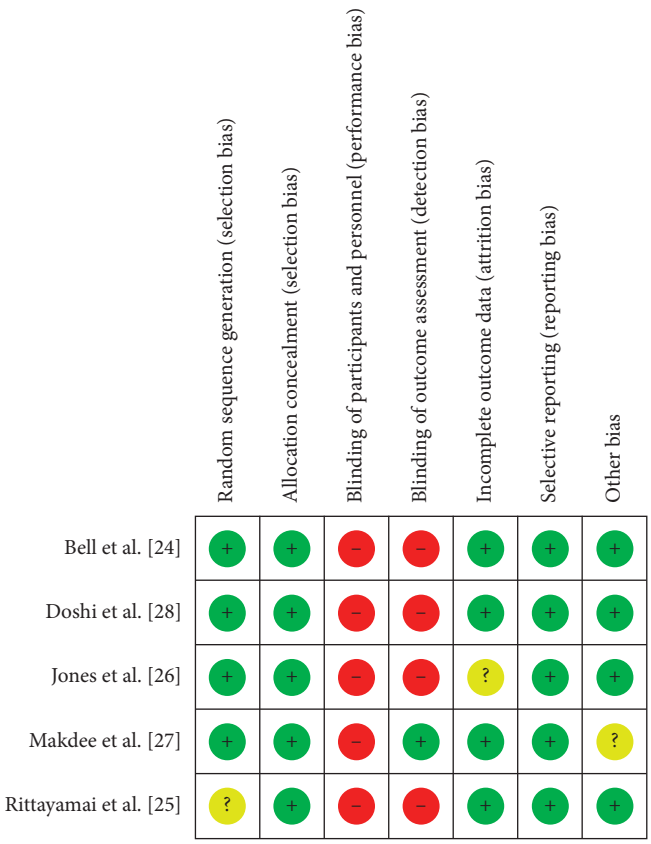


Figure 2: Risk of bias summary.

reduction in the Borg score. Both arms showed a significant decrease in the dyspnea level in the HFNC group (reduction in the respiratory rate >20% from baseline: HFNC 32/48 (66.7%), COT 20/52 (38.5%), $p = 0.005$; reduction in the Borg score: HFNC 36/48 (75%), COT 29/52 (55.8%), $p = 0.044$).

4.4.5. Comfort Score. Because different scoring systems, including a 5-point Likert scale, numerical rating scale, and visual analog scale, were used in different RCTs, we calculated SMDs to evaluate patient comfort levels. Three of the 4 RCTs reported measurable comfort scores, and patients in the HFNC group were more comfortable than those in the COT group (SMD −0.76 SD, 95% CI −1.01 to −0.51) (Table 2).

5. Discussion

The most important result of this meta-analysis is that HFNC therapy for ARF patients in EDs can reduce the need for escalation oxygen therapy compared with COT. This result was similar to that in recent meta-analyses [17, 29, 30]. Although there were no differences found in the mortality rate, there was a decreasing trend between HFNC therapy and intubation rate in ARF patients, despite the lack of statistical significance. On the other hand, we did not observe an influence of HFNC therapy on the ICU admission rate, ED discharge rate or length of ED/hospital stay. A meta-analysis by Maitra et al. [31], which included 5 trials ($n = 759$), revealed no difference in the requirement of increased respiratory support between the HFNC therapy and COT groups. However, the study enrolled not only ARF patients but also postcardiac operation patients, and the heterogeneity was high. In addition, Rochwerg et al. [17], Monro–Somerville et al. [19], Bocchile et al. [30] who conducted 3 previous meta-analyses including 7 trials ($n = 1647$), 8 trials ($n = 1567$), and 6 trials ($n = 839$), respectively, demonstrated that HFNC therapy significantly reduced the intubation rate compared to COT. In our study, we did not observe an apparently reduced intubation rate in the HFNC group, probably because of the low patient number.

The other important result of this meta-analysis is that treating ARF patients with HFNC therapy resulted in lower patient dyspnea scores and higher patient comfortable than treating ARF patients with COT. All of our included RCTs revealed that HFNC therapy was better than COT regarding dyspnea and comfort scores, except for 1 RCT [26]. This RCT by Jones et al., which used a 5-point Likert scale to evaluate patient dyspnea and comfort levels, present the results by combining the best 2/other 3 or worst 2/other 3 categories for positive and negative questions, respectively, so we were not able to quantitatively pool these data. HFNC therapy can provide warmed, humidified, and 100% oxygen, which may explain the reduction in the need for escalation oxygen therapy compared to COT. Other features such as removing airway dead space, improving oxygenation, optimizing mucosal functions, maximizing mucociliary clearance, promoting expectoration, and decreasing interruptions to oxygen therapy are also possible reasons for the decreasing trend in the intubation rate, improved patient dyspnea scores, and improved comfort levels associated with HFNC therapy.

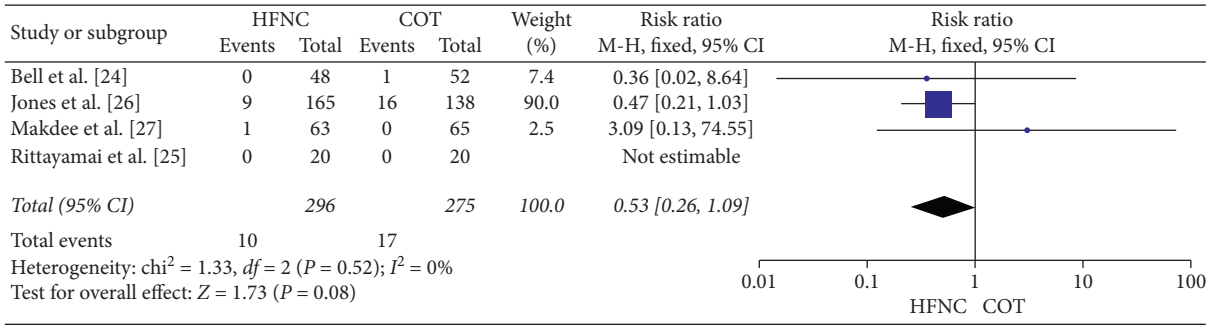
In this study, we noted that some targeted studies are heterogeneous with their methods and case mix. For example, three RCTs [24–26] included all kinds of ARF patients (COPD, pneumonia, cardiac-related disease, and others) while 1 RCT [27] only included cardiogenic pulmonary edema patients. In addition, initial FiO_2 (ranged from 28% to 100%), flow rate (ranged from 35 L/min to 50 L/min) of HFNC, duration of therapy (ranged from 1 hour to 9.3 hours), and authors' definitions of ARF were all different. Although the inclusion studies were heterogeneous, most of the outcomes did not reveal statistical heterogeneity (I_2 or inconsistency). The FiO_2 and the flow rate needed to titrate to clinical demand in all including patients. Moreover, most improvements in respiratory effort and oxygenation were already obtained at the flow rate of 30 L/min [32]. These are possible reasons to explain consistency of most outcomes despite different cause of ARF and initial settings.

HFNC also plays an important role in acute exacerbations of chronic obstructive pulmonary disease (AECOPD). AECOPD with respiratory failure, a kind of type II

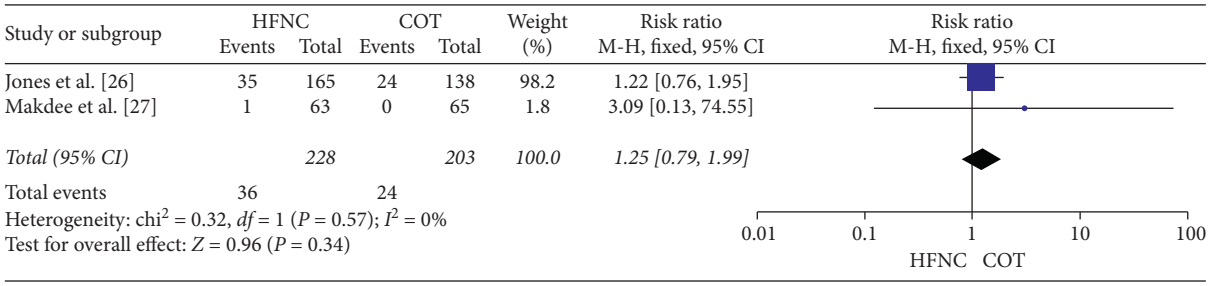
Table 2: The summary of outcomes and GRADE quality assessments.

Quality assessment							No of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consideration	HFNC	COT	Relative RR (95% CI)	Absolute (95% CI)		
Intubation rate												
4	RCTs	Serious[a]	Not serious	Not serious	Serious[b]	None	10/296 (3.4%)	17/275 (6.2%)	0.53(0.26–1.09)	−32 per 1000 (from −69 to 4)	⊕⊕Low	Critical
Mortality rate												
2	RCTs	Not serious	Not serious	Not serious	Serious[b]	None	36/228 (15.8%)	24/203 (11.8%)	1.25(0.79–1.99)	32 per 1000 (from −32 to 95)	⊕⊕⊕Moderate	Critical
ICU admission rate												
2	RCTs	Not serious	Not serious	Not serious	Serious[b]	None	17/213 (8%)	15/190 (7.9%)	1.11(0.58–2.12)	8 per 1000 (from −43 to 59)	⊕⊕⊕Moderate	Critical
ED discharge rate												
2	RCTs	Not serious	Not serious	Not serious	Serious[b]	None	23/111 (20.7%)	23/117 (19.7%)	1.04(0.63–1.72)	8 per 1000 (from −93 to 109)	⊕⊕⊕Moderate	Critical
Need for escalation												
4	RCTs	Serious[a]	Not serious	Not serious	Not serious	None	13/296 (4.4%)	29/275 (10.5%)	0.41(0.22–0.78)	−62 per 1000 (from −105 to −19)	⊕⊕⊕Moderate	Critical
Length of ED stay (hour)												
3	RCTs	Not serious	Serious[c]	Not serious	Serious[b]	None	276	255	—	MD 1.66 hours (from −0.95 to 4.27)	⊕⊕Low	Critical
Length of hospital stay (day)												
2	RCTs	Not serious	Serious[c]	Not serious	Serious[b]	None	228	203	—	MD 0.9 days (from −2.06 to 3.87)	⊕⊕Low	Critical
Patient dyspnea score												
2	RCTs	Serious[d]	Serious[c]	Not serious	Not serious	None	83	85	—	MD −0.82 point (from −1.45 to −0.18)	⊕⊕Low	Critical
Patient comfort score												
3	RCTs	Serious[d]	Not serious	Not serious	Not serious	None	131	137	—	SMD −0.76 SD (from −1.01 to −0.51)	⊕⊕⊕Moderate	Critical

RCT, randomized controlled trial; HFNC, high-flow nasal cannula; COT, conventional oxygen therapy; CI, confidence interval; RR, risk ratio; MD, mean difference; SMD, standardized mean difference. [a]All inclusion trials lacked blinding (performance bias), so escalation or intubation may be subjective. [b]Insufficient evidence of clear benefit or harm because of a wide CI. [c]Significant heterogeneity among the included trials ($I^2 > 50\%$). [d]Subjective outcome. ⊕, very low quality; ⊕⊕, low quality; ⊕⊕⊕, moderate quality; ⊕⊕⊕⊕, high quality.



(a)



(b)

Figure 3: Intubation rate and mortality rate. (a) Intubation rate: HFNC group versus COT group. (b) Mortality rate: HFNC group versus COT group.

respiratory failure, is caused by airflow obstruction or increasing dead space. As previously mentioned, HFNC can generate about 2–4 cm H_2O positive end-expiratory pressure [33], resulting in decreasing PaCO2 level and improving oxygenation by elimination of some airway dead space [13]. Furthermore, titrated oxygen therapy with target saturation of 88–92% can significantly reduce mortality, hypercapnia, and respiratory acidosis in AECOPD [34]. HFNC is able to deliver a constant and wide FiO_2 range oxygen, so it can titrate with target saturation of 88–92% depending on clinical needs. According to the 2019 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline, HFNC may be an alternative to standard oxygen therapy or noninvasive positive pressure ventilation in AECOPD [35]. There are also some investigations demonstrate using HFNC in COPD patients can decrease PaCO2 level [36], respiratory effort, and improving oxygenation [37]. Thus, applying HFNC to AECOPD patients is reasonable respiratory support.

There was a decreasing trend between HFNC therapy and intubation rate in ARF patients, but there were no differences found in the mortality rate. There was a concern about that delay intubation could increase mortality in ARF patients treating with HFNC. Because HFNC could improve respiratory effort and patients "looked" better initially, they would not be intubated in a timely manner. Kang et al. illustrated failure of HFNC therapy may delay intubation and increase mortality [38]. However, the "delay" was defined as >48 hours after HFNC therapy, which was far from our included RCTs (ranged from 1 hour to 9.3 hours). In addition, there were various etiologies of ARF, such as COPD, pneumonia, pulmonary edema, asthma, pulmonary embolism, and other causes, in the included RCTs. Not every disease initially benefited equally from HFNC therapy. Messika et al. demonstrated that increased breathing frequency, an increased Simplified Acute Physiology Score (SAPS) II score, and decreased PaO_2/FiO_2 were associated with HFNC treatment failure [39].

To the best of our knowledge, this is the first meta-analysis regarding the use of HFNC for ARF patients in EDs. The advantages of this analysis include performing a comprehensive article search in 3 databases (PubMed, EMBASE, and the Cochrane Library). In addition, only RCTs involving HFNC therapy, COT or NIV for de novo acute hypoxemic respiratory failure patients in EDs were included in our meta-analysis. Moreover, we used the GRADE method to evaluate the quality of evidence for primary and secondary outcomes. There were also several limitations to this study. Firstly, the number of RCTs comparing HFNC to COT or NIV for patients with ARF in EDs were too few to include in our meta-analysis, so we were not able to perform subgroup analyses, and the low patient number increased the risk of bias. Secondly, our quality of evidence for outcomes was low to moderate and was affected by serious risk of bias, inconsistencies, and imprecision. Finally, we did not have enough power to evaluate publication bias by inspection of a funnel plot because of the small sample size. Therefore, further large-sample studies are warranted to clarify the role of HFNC therapy for ARF patients in EDs.

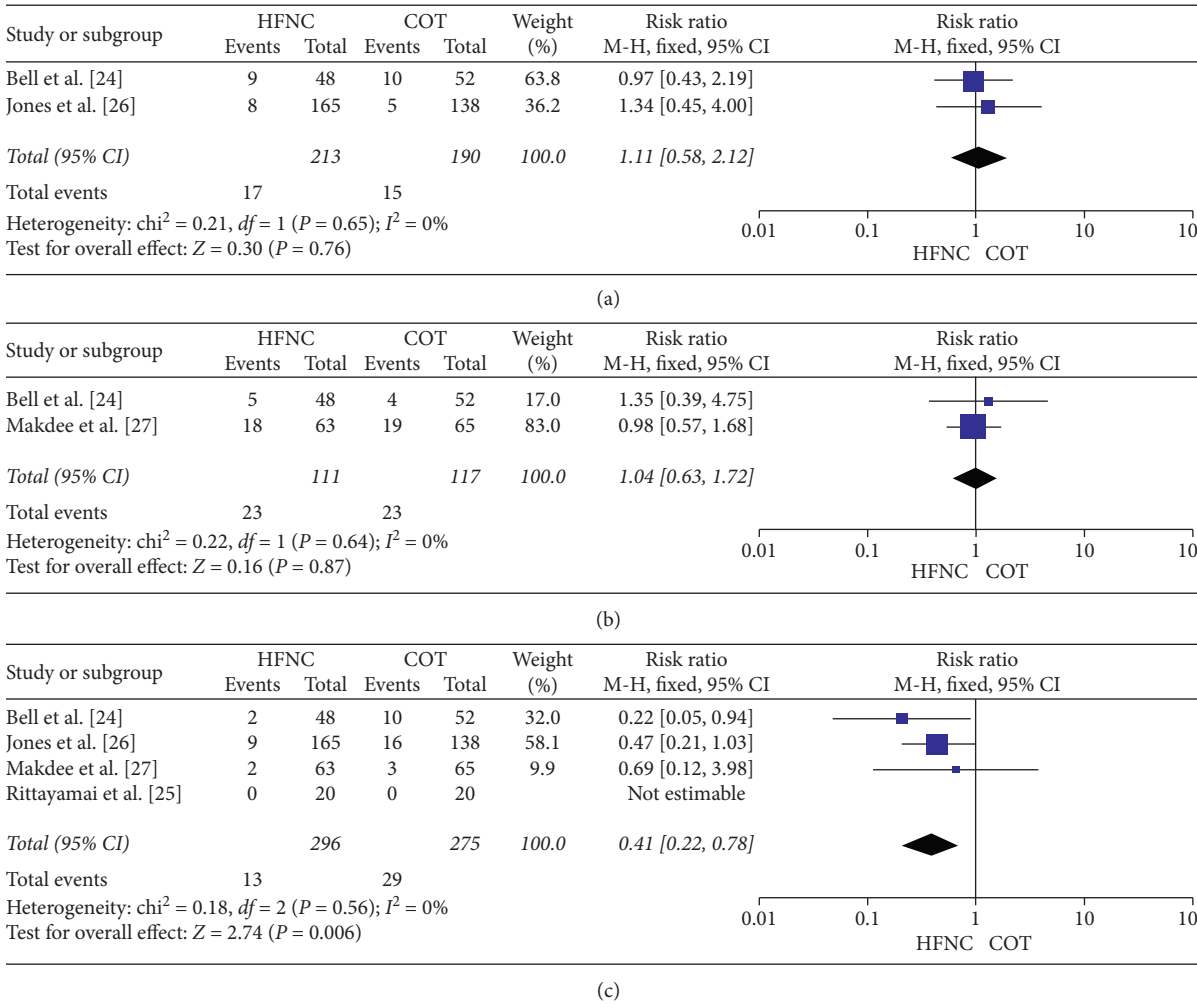


Figure 4: Other secondary outcomes. (a) ICU admission rate: HFNC group versus COT group. (b) ED discharge rate: HFNC group versus COT group. (c) Need for escalation: HFNC group versus COT group.

6. Conclusion

In this meta-analysis, we demonstrated that HFNC therapy for ARF patients in the ED might decrease the intubation rate compared to COT. In addition, it can decrease the need for escalation, decrease the patient's dyspnea score, and increase the patient's comfort level compared to COT. Further high-quality and large-sample studies are warranted to confirm the role of HFNC therapy for ARF patients in EDs.

Data Availability

All data are available for all users. We comprehensively searched 3 databases (PubMed, EMBASE, and the Cochrane Library) for articles published from database inception to 12 July 2019. Only randomized controlled trials (RCTs) were conducted in EDs and HFNC therapy was compared to COT or NIV.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Supplementary Materials

A visual inspection of the funnel plot revealed no publication bias. (*Supplementary Materials*)

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Research Article

Prognostic Value of Serum Albumin at Admission for Neurologic Outcome with Targeted Temperature Management after Cardiac Arrest

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Introduction. It is well known that hypoalbuminemia is associated with adverse outcomes in various critical illnesses. However, there are few studies specifically measuring the association between albumin level and neurologic outcomes after CA treated with TTM. The aim of this study was to assess whether serum albumin concentration on admission had prognostic value for OHCA patients treated with TTM. *Methods*. We included adult patients aged ≥18 years with nontraumatic OHCA treated with TTM whose serum albumin concentration was available and who were admitted from 2009 to 2016. Serum albumin was measured within 1 h after ROSC, and hypoalbuminemia was defined as admission serum albumin <3.5 g/dl. A good neurologic outcome was defined as a cerebral performance category score of 1 or 2 at 6 months. *Results*. A total of 255 patients were eligible for analysis, of whom 106 (41.6%) survived to 6 months; 84 (32.9%) of these patients achieved favorable neurologic outcomes. The mean albumin values were significantly lower in patients with poor neurologic outcomes than the values in those with good neurologic outcomes (3.3 ± 0.6 vs. 3.9 ± 0.4, respectively, $p < 0.001$). After adjusting the crude model, patients in the hypoalbuminemia group were 3.5 times more likely to have poor neurologic outcome than were those in the normal albumin group (OR 3.526, 95% CI 1.388–8.956, $p = 0.008$). *Conclusions*. Hypoalbuminemia was common after CA, and the serum albumin level at admission was associated with poor neurological outcomes at 6 months after CA in patients treated with TTM.

1. Introduction

Cardiac arrest (CA) is a health problem worldwide and is associated with high rates of mortality and morbidity [1]. Although the major pathophysiologic mechanisms after CA have not yet been elucidated, systemic inflammation after ischemic reperfusion injury contributes to hypoxic brain injury, the major leading cause of death after CA [2]. To protect the brain and other critical organs from systemic inflammation, targeted temperature management (TTM) at 32–36 for 24 hrs is considered the standard of care after CA [3–5]. Optimizing cardiopulmonary function and minimizing reperfusion injury should be focused during post-cardiac arrest care [6].

Albumin is the main protein of human plasma, playing several important physiologic roles, including maintenance of plasma oncotic pressure and microvascular integrity and regulating vascular functions, antioxidant activities, and anticoagulant effects [7–9]. The systemic inflammatory response has been associated with decreased synthesis and increased catabolism of albumin [10]. Hypoalbuminemia has been shown to increase blood viscosity and cause endothelial dysfunction [11–13]. It is well known that hypoalbuminemia is associated with adverse outcomes in various

critical illnesses, especially cardiovascular disease, stroke, sepsis, and coronary artery bypass grafting [14–18]. However, there are few studies specifically measuring the association between the albumin level and neurologic outcomes after CA with TTM.

Therefore, the aim of this study was to test the hypothesis that the serum albumin level on admission was associated with neurological outcomes of out-of-hospital CA patients treated with TTM. We combined this association with other clinical variables to assess the value of albumin in predicting neurological outcomes.

2. Materials and Methods

2.1. Study Population. This retrospective analysis using prospectively collected data was conducted at the Seoul St. Mary's Hospital, a tertiary urban teaching hospital, from 2009 to 2016. Our institutional review board approved this study. The requirement for informed consent was waived because of the retrospective nature of this study. All comatose patients who were resuscitated and brought to the emergency department were treated with post-cardiac arrest care protocols including TTM [19]. The inclusion criteria were as follows: older than 18 years of age; resuscitated from out-of-hospital CA and treated with TTM; and having an albumin level measured within 1 hr after ROSC. Patients were excluded if the cardiac arrest was caused by trauma or if TTM was not initiated or was interrupted due to hemodynamic instability, recurrent lethal arrhythmia, or severe bleeding.

2.2. Clinical Variables. The study participants' medical records were reviewed. The following demographic and clinical data were collected for each patient: age, sex, preexisting disease (e.g., hypertension, diabetes mellitus, coronary artery disease, renal disease, liver disease, stroke, and malignancy), cause of arrest, witnessed collapse, bystander cardiopulmonary resuscitation (CPR), rhythm initially presenting after arrest, time from collapse to restoration of spontaneous circulation (ROSC), post-ROSC neurologic examinations (e.g., pupillary light reflex (PLR), self-respiration, and Glasgow Coma Scale (GCS)), hemodynamic status, and length of stay. Definitions were based on Utstein-style guidelines [20]. Serum albumin was measured within 1 h after ROSC, and hypoalbuminemia was defined as admission serum albumin <3.5 g/dl.

2.3. Outcome. The primary outcome of this study was 6-month neurologic outcome. Neurologic outcome was assessed using the cerebral performance category (CPC) score [21]. The five categories of the CPC are as follows: CPC 1, conscious and alert with good cerebral performance; CPC 2, conscious and alert with moderate cerebral performance; CPC 3, conscious with severe cerebral disability; CPC 4, comatose or in persistent vegetative state; and CPC 5, brain dead, circulation preserved, or death at discharge. Favorable neurologic outcomes were defined as CPC scores of 1 and 2.

2.4. Statistical Analysis. We tested the distributions of the continuous variables for normality using visual inspection and the Shapiro–Wilk test. Normally distributed data were expressed as the means and standard deviations using Student's t-test. Nonnormally distributed data were assessed using the Mann–Whitney U test. Categorical variables were presented as frequency with percentage and were compared using the χ^2 test or Fisher's exact test, as appropriate. Multivariate binary logistic regression analysis was used to assess independent predictors of 6-month poor neurologic outcome. All variables with a significance level <0.1 by univariate analysis were entered into the multivariate logistic regression model to create a crude model. The factors with p values < 0.05 on the multivariate logistic regression model were entered into a crude model. We considered factors in the crude model as established risk factors because no confirmed risk factors exist for predicting 6-month poor neurologic outcome. To evaluate the association of serum albumin with 6-month poor neurologic outcome, the serum albumin values were divided into 2 categories using the following cutoff values: <3.5 mg/dl and ≥3.5 mg/dl. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated with the lowest quartile as the reference. Serum albumin was examined as a continuous variable as well. All statistical analyses were performed using SPSS software, version 17.0 (SPSS, Chicago, IL, USA). Values of $p < 0.05$ were considered statistically significant for all comparisons.

3. Results

3.1. Characteristics of the Study Population. During the study period, a total of 410 consecutive patients with nontraumatic out-of-hospital cardiac arrest (OHCA) were admitted to our ED. Sixty-six patients did not receive TTM, 7 had no serum albumin data, and 255 were eligible for our analyses, of whom 106 (41.6%) survived to 6 months; 84 (32.9%) achieved favorable neurologic outcomes.

The mean patient age was 54.7 ± 16.2 years, and 180 patients (71%) were male; 107 patients (42.0%) died during their hospital stay, and the mean serum albumin level was 3.5 ± 0.6 mg/dl. Table 1 presents the characteristics and preresuscitation and postresuscitation data of eligible patients. The hypoalbuminemia group had a higher proportion of older age and history of diabetes or renal disease and had a longer time from collapse to ROSC. The hypoalbuminemia group was less likely to have first documented shockable rhythm and positive results for post-ROSC neurologic examination (e.g., PLR, GCS motor, and self-respiration). The mean arterial pressure immediately after ROSC was significantly lower in the hypoalbuminemia group than that in the normal albumin group. Regarding outcomes, the normal serum albumin group had the highest proportion of favorable neurological outcome and 6-month survival (Table 1).

3.2. Univariate and Multivariate Analysis of Factors Associated with 6-Month Neurologic Outcome. The mean albumin values were significantly lower in the poor neurologic

Table 1: Baseline characteristics between patients with and without admission hypoalbuminemia.

	Hypoalbuminemia (<3.5 g/dl, $n = 109$)	Normal serum albumin (≥3.5 g/dl, $n = 146$)	p
Demographics			
Male	76 (69.7)	104 (71.2)	0.794
Age, years	61.7 ± 15.9	49.5 ± 15.3	<0.001
Comorbidities			
CAD	12 (11.0)	19 (13.0)	0.628
CHF	2 (1.8)	6 (4.1)	0.472
Stroke	3 (2.8)	2 (1.4)	0.654
Hypertension	40 (36.7)	36 (24.7)	0.038
Diabetes mellitus	36 (33.0)	19 (13.0)	<0.001
Renal disease	14 (12.8)	3 (2.1)	0.001
Liver disease	2 (1.8)	0 (0.0)	0.182
Malignancy	7 (6.4)	4 (2.7)	0.213
Resuscitation variables			
Cardiac cause	71 (65.1)	104 (71.2)	0.299
Shockable rhythm	23 (21.1)	75 (51.4)	<0.001
Witnessed	75 (68.8)	107 (73.8)	0.383
Bystander CPR	56 (51.4)	86 (59.3)	0.207
Anoxic time (min)	37.4 ± 18.3	30.9 ± 20.7	0.009
Post-ROSC N/Ex			
PLR	26 (23.9)	69 (47.3)	<0.001
Self-respiration	41 (37.6)	90 (61.6)	<0.001
GCS motor, yes	14 (12.8)	46 (31.5)	<0.001
Hemodynamic status			
MAP	83.9 ± 26.9	97.1 ± 25.5	<0.001
HR	100.9 ± 28.3	105.0 ± 26.9	0.234
Temperature	35.3 ± 1.6	35.8 ± 1.0	0.005
Outcomes			
Pneumonia	56 (51.4)	53 (36.3)	0.016
Septic shock	10 (9.2)	16 (11.0)	0.641
HD (days)	7.0 (3.0–20.0)	12.0 (6.0–20.0)	0.005
6-month mortality	90 (82.6)	59 (40.4)	<0.001
6-month poor neurologic outcome	95 (87.2)	76 (52.1)	<0.001

CAD, coronary artery disease; CHF, congestive heart failure.

outcome group than in the good neurologic outcome group (3.3 ± 0.6 vs. 3.9 ± 0.4, respectively; $p < 0.001$) (Table 2). On univariate analysis, age, history of HTN, diabetes mellitus, renal disease and malignancy, cause of arrest, initial documented rhythm, witnessed collapse, and time from collapse to ROSC, PLR, self-respiration, and GCS motor, mean arterial pressure, and temperature were all significantly associated with 6-month neurologic outcome. Variables with p values < 0.1 on univariate analysis were entered into the multivariate logistic regression model to create a crude model, and the factors with p values < 0.05 in the multivariate logistic regression model were entered into the crude model. The crude model included the following variables: cardiac etiology, initial rhythm, time from collapse to ROSC, and GCS motor.

After adjusting the crude model, albumin levels still showed an association with 6-month poor neurologic outcome. Patients in the hypoalbuminemia group were 3.5 times more likely to have poor neurologic outcome than were those in the normal albumin group (Model I, Table 3). After adjusting the crude model and history of liver disease, renal disease, and malignancy, this association remained. Furthermore, patients in the hypoalbuminemia group were 2.7 times more likely to have poor neurologic outcome than were those in the normal albumin group (model II, Table 3). When serum album was examined as a continuous variable, there were significant associations with 6-month poor neurologic outcome after adjusting for model I covariates (OR = 0.222, 95% CI = 0.095–0.516) and after model II covariates (OR = 0.275, 95% CI = 0.116–0.651) (Table 3). These findings suggested that there was 77.8% and 72.8% more favorable neurologic outcome for every 1 mg/dl of serum albumin (Table 3).

3.3. Prognostic Value of Hypoalbuminemia. Kaplan–Meier analysis revealed that the survival rate of patients with hypoalbuminemia was significantly lower than in those with serum albumin levels at or above 3.5 g/dL ($p < 0.001$; Figure 1).

In receiver operating characteristic (ROC) curve analysis, the area under the curve (AUC) of crude model I was 0.930 (95% CI 0.892–0.958). Figure 2 shows the AUCs combined with hypoalbuminemia in crude models I and II (AUC 0.938 for crude model I with hypoalbuminemia and 0.944 for crude model II with hypoalbuminemia).

Table 2: Comparison of patients according to 6-month neurologic outcome.

	Good neurologic outcome ($n = 84$)	Poor neurologic outcome ($n = 171$)	p
Demographics			
Male	64 (76.2)	116 (67.8)	0.169
Age, years	48.3 ± 15.2	57.9 ± 16.5	<0.001
Comorbidities			
CAD	12 (14.3)	19 (11.1)	0.466
CHF	3 (3.6)	5 (2.9)	0.721
Stroke	0 (0.0)	5 (2.9)	0.175
Hypertension	16 (19.0)	60 (35.1)	0.008
Diabetes mellitus	5 (6.0)	50 (29.2)	<0.001
Renal disease	0 (0.0)	17 (9.9)	0.001
Liver disease	0 (0.0)	2 (1.2)	0.449
Malignancy	1 (1.2)	10 (5.8)	0.074
Resuscitation variables			
Cardiac cause	79 (94.0)	96 (56.1)	<0.001
Shockable rhythm	68 (81.0)	30 (17.5)	<0.001
Witnessed	72 (85.7)	110 (64.7)	<0.001
Bystander CPR	52 (61.9)	90 (52.9)	0.176
Anoxic time (min)	23.6 ± 15.0	38.6 ± 20.3	<0.001
Post-ROSC N/Ex			
PLR	64 (76.2)	31 (18.1)	<0.001
Self-respiration	73 (86.9)	58 (33.9)	<0.001
GCS motor, yes	47 (56.0)	13 (7.6)	<0.001
Hemodynamic status			
MAP	99.2 ± 25.2	87.6 ± 26.9	0.001
HR	101.2 ± 25.7	104.3 ± 28.4	0.407
Temperature	35.8 ± 0.9	35.5 ± 1.4	0.060
Hypoalbuminemia	14 (16.7)	95 (55.6)	<0.001
Albumin (mg/dl)	3.9 ± 0.4	3.3 ± 0.6	<0.001
Outcomes			
Pneumonia	26 (31.0)	83 (48.5)	0.008
Septic shock	4 (4.8)	22 (12.9)	0.049
HD (days)	7 (4–20)	15 (9–23)	<0.001

Table 3: Odds ratios for hypoalbuminemia in the prediction of 6-month poor neurologic outcome.

	OR (95% CI)	p	Adjusted OR (95% CI)	p
Hypoalbuminemia	6.250 (3.268–11.951)	<0.001		
Crude model I			3.526 (1.388–8.956)	0.008
Crude model II			2.658 (1.017–6.949)	0.046
Serum albumin (mg/dl)	0.138 (0.073–0.262)	<0.001		
Crude model I			0.222 (0.095–0.516)	<0.001
Crude model II			0.275 (0.116–0.651)	0.003

Crude model I: cardiac etiology + initial rhythm + anoxic time + GCS motor score. Crude model II: crude model I + liver disease + kidney disease + malignancy.

4. Discussion

The main finding of this study was that hypoalbuminemia immediately after ROSC was common and was associated with neurologic outcome at 6 months after CA in patients treated with TTM. This association persisted after adjusting for patient-level covariates. However, we could not identify whether correction of hypoalbuminemia improved patient outcome.

Albumin is synthesized in the liver and has a half-life of approximately 3 weeks, and an albumin concentration less than 3.5 g/dl is generally referred to as hypoalbuminemia. Albumin plays important physiologic functions, and hypoalbuminemia is a well-known risk factor for coronary artery disease, acute myocardial infarction, heart failure, stroke, and sepsis [14–17, 22]. In addition, albumin is an indirect indicator of nutritional status. Matsuyama et al. first reported that a higher serum albumin concentration at hospital admission was associated with favorable neurologic outcome after OHCA in a concentration-dependent manner [23]. However, the authors could not analyze the underlying diseases of individual patients (e.g., chronic renal disease) that are commonly associated with hypoalbuminemia.

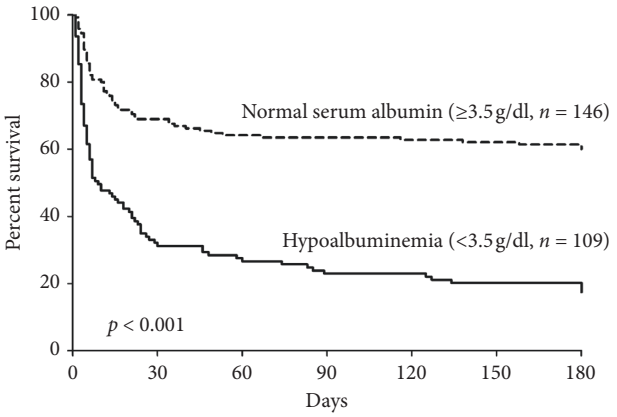

Figure 1: 180-day Kaplan–Meier survival analysis over time stratified by serum albumin level.

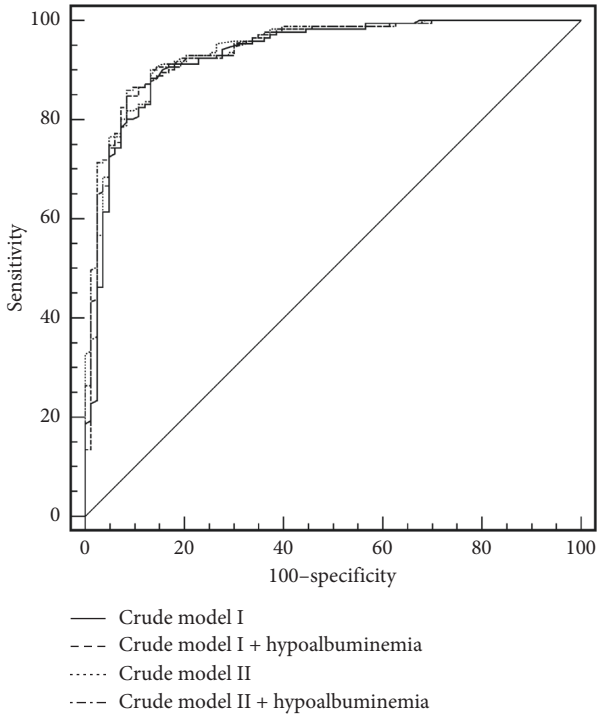

Figure 2: Prognostic value of hypoalbuminemia for the prediction of 6-month poor neurologic outcome. (1) Crude model I (AUC 0.930, 95% CI 0.892–0.958). (2) Crude model I with hypoalbuminemia (AUC 0.938, 95% CI 0.901–0.965). (3) Crude model II (AUC 0.940, 95% CI 0.903–0.966). (4) Crude model II with hypoalbuminemia (AUC 0.944, 95% CI 0.908–0.969).

There are several possible underlying mechanisms explaining the relationship between hypoalbuminemia and poor neurologic outcomes in OHCA patients treated with TTM. First, the most important pathophysiologic mechanism leading to morbidity and mortality after CA is systemic inflammation after ischemic reperfusion injury. Albumin is known as a negative acute-phase protein whose concentration decreases in response to inflammation [10]. Therefore, a low serum-albumin level could be a marker of severe systemic inflammatory responses that could lead to worse outcomes after CA. Second, another possible link between hypoalbuminemia and poor neurologic outcomes in patients with CA treated with TTM is oxidative stress. Albumin constitutes the major plasma protein target of oxidative stress because of reactive oxygen species [24]. Albumin contains a rich thiol group that accounts for 80% of total thiol in plasma-depleting reactive oxygen species [25]. For this reason, reduced serum albumin may be associated with increased oxidative stress conditions. Third, serum albumin is one of the biochemical markers of nutritional status. Serum albumin is closely correlated with the degree of malnutrition, considered a general risk factor in critically ill conditions. Finally, albumin has neuroprotective properties. Experimental studies showed that human albumin administration was highly neuroprotective in reducing infarct volume and cerebral edema in animals with acute stroke [26–28]. Despite the fact that clinical trials have failed to show efficacy of human serum albumin administration after acute ischemic stroke, further studies should be performed to prove the neuroprotective effect of human serum albumin [29].

In our study, the hypoalbuminemia group was older than the normal serum albumin group was and had longer anoxic time, lower incidence of initial shockable rhythm, lower mean arterial blood pressure, and higher incidence of pneumonia than did the normal serum albumin group. Although the exact mechanism could not be explained in this study, it is thought that the abovementioned various hypotheses are a synthesized result. Chronic renal disease, known as an independent risk factor for mortality after CA, was more common in the hypoalbuminemia group. Although we adjusted for chronic renal disease in the multivariate logistic regression model, this factor could affect neurological outcomes after CA with TTM.

This study has several limitations. First, this was a single-center study, which limits the generalizability of our findings. Second, only albumin levels at the time of admission were analyzed, and subsequent albumin levels were not analyzed. In addition, we could not determine whether albumin replacement was performed in the hypalbuminemia group, and we do not know whether albumin replacement improved neurologic prognosis. Third, most patients in our cohort were managed with TTM at 33°C for 24 h regardless of their initial rhythm, and our finding may thus not be applicable to other management strategies.

5. Conclusion

Hypoalbuminemia was common after CA, and the serum albumin level at admission was associated with poor neurological outcomes at 6 months after CA in patients treated with TTM. Further studies should be performed to determine whether the correction of hypoalbuminemia improves neurological outcomes.

Data Availability

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

Ethical Approval

The study was approved by the Institutional Review Board of the Catholic University of Korea at Seoul Saint Mary's Hospital and conducted with a waiver of patient consent because of the noninterventional, retrospective design of the study.

Conflicts of Interest

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

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Research Article

The Use of Catheter Mount Will Result in More Reliable Carbon Dioxide Monitoring under Fluid Exposing Conditions

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Introduction. Capnometer can be readily malfunctioned by fluid exposure during treatment of critically ill patients. This study aimed to determine whether placing capnometer distant from the endotracheal tube by connecting direct connect catheter mount (DCCM) is effective in yielding reliable end-tidal carbon dioxide ($ETCO_2$) by reducing capnometer malfunctioning caused by water exposure. *Methods*. In 25 healthy adults, a prospective, open label, crossover study was conducted to examine the effect of DCCM in mainstream and microstream capnometers under water exposing conditions. The primary endpoint was the comparison of $ETCO_2$ between proximal DCCM (pDCCM) and distal DCCM (dDCCM). *Results*. For mainstream capnometers, mean $ETCO_2$ was significantly ($p < 0.001$) higher in dDCCM compared to pDCCM under water exposing conditions (29.5 vs. 19.0 with 5 ml; 33.8 vs. 21.2 with 10 ml; mmHg). Likewise, for microstream capnometers, $ETCO_2$ was greatly higher ($p < 0.001$) in dDCCM compared to pDCCM (30.5 vs. 13.9 with 5 ml; 29.9 vs.11.4 with 10 mL; mmHg). $ETCO_2$ measured by dDCCM was reliable in microstream settings, whereas it was unreliable in mainstream (correlation coefficient 0.88 vs. 0.27). *Conclusions*. Application of DCCM onto the capnometer setting seems to be effective in reducing capnometer malfunctioning under fluid exposing conditions, which is obvious in microstream capnometer by producing more reliable $ETCO_2$.

1. Introduction

Capnometer is a device that measures end-tidal carbon dioxide ($ETCO_2$) by infrared sensor [1, 2]. Capnometer has been widely used to monitor proper placement of endotracheal tube (ETT) and status of ventilation [3, 4]. According to the 2010 American Heart Association (AHA) and European Resuscitation Council (ERC) guidelines, the use of capnometer is recommended during cardiopulmonary resuscitation (CPR), in order to evaluate quality of CPR and detect recovery of spontaneous circulation (ROSC) in intubated patients [5, 6]. During CPR, while low $ETCO_2$ (<10 mmHg) represents poor quality of CPR, a dramatic increase of $ETCO_2$ (up to 35-40 mmHg) indicates the occurrence of ROSC [6–8]. Accurate assessment of $ETCO_2$ is therefore essential to monitor placement of ETT and quality of CPR.

Nevertheless, reliable $ETCO_2$ measurement by capnometer is difficult in clinical settings. $ETCO_2$ measurement becomes readily unreliable when capnometer is vulnerable to fluid exposure through ETT, mostly in cases of wet lung conditions [1, 4]. In wet lung conditions, fluid produced by patients is present in ETT, which interferes the infrared sensor on capnometer with detecting CO_2 absorption at 4.3 μm wavelength, resulting in under- or oversensing $ETCO_2$ values. Furthermore, the sampling line connected to sidestream capnometer (i.e., microstream capnometer) is often occluded by condensed particles of fluid sourced from patients [1, 4]. Therefore, clinical settings of which patients

have wet lung conditions often render capnometer exposed to fluid through ETT, leading to higher chances of capnometer malfunctioning.

To achieve accurate $ETCO_2$ measurement, it is imperative for capnometer to avoid fluid contact and in that perspective, placing capnometer away from ETT is necessary. The direct connect catheter mount (DCCM, RT021 catheter mount, Fisher & Paykel Healthcare Ltd., Auckland, NZ) is a tubing system commonly inserted between breathing circuit and ETT to provide this connection with flexibility and a resultant reduction in extubation risk [9]. However, it can also be placed between ETT and capnometer to make them separate away, which could help capnometer avoid fluid contact supplied from patients.

The purpose of this study was to investigate whether placing capnometer away from ETT via DCCM insertion is effective in yielding reliable $ETCO_2$ by protecting capnometer against water contact. We hypothesized that the use of DCCM will reduce capnometer malfunction, leading to reliable $ETCO_2$ monitoring.

2. Materials and Methods

2.1. Study Design and Recruitment. A prospective crossover study was conducted at Hanyang University Medical Center in Seoul, Republic of Korea, on March 17, 2014. The study protocol was approved by the Institutional Review Board (IRB) of the Hanyang University Guri Hospital (Approval date: March 2014; Reference no. 2013-68). Recruitment was performed on March 9 - 16, 2014, and 25 healthy adults who submitted their written consent forms were included in the study. All patients were recruited after IRB approval and registration with clinicaltrials.gov.

2.2. Protocols. Two different sets of capnometers were tested in the study: mainstream capnometer vs. microstream capnometer. Two capnometers for each set were installed at proximal and distal ends of DCCM. For both settings, capnometers installed on proximal DCCM (pDCCM) were directly linked to ETTs, being free from the DCCM effect, whereas those on distal DCCM (dDCCM) were under the DCCM effect. In this study, hence, four test groups were designed: (1) mainstream-pDCCM; (2) mainstream-dDCCM; (3) microstream-pDCCM; and (4) microstream-dDCCM (Figure 1).

Prior to the study, all participants were provided with 5 min oral instructions on breathing techniques. During inspiration, participants were asked to inhale through nose only, not allowing them to open their mouth and swallow water. During expiration, however, they were forced to occlude their nose and exhale forcefully only through mouth when exposed to the water-sprayed ETT. Participants were also asked to breathe regularly according to the metronome sound (15 beats per min), which was made by the Micro Metronome application (SPACEWARE Inc., Android apps on Google Play) installed on the smart phone (LG Optimus G Pro, LG Electronics, Seoul, Republic of Korea).

All participants (n=25) used one of the mainstream and microstream capnometers and then the other capnometer. They were instructed to hold the ETT cuffs by their mouth and breathe for 2 min each time when the ETT was sprayed with 0 (baseline), 5, or 10 ml distilled water, in turn, which were given to the ETT just before connecting with pDCCM. Five min intervals were given for each time of breathing. The water sprayed within the ETT was allowed to contact capnometers freely when participants were exhaling. During crossovers, 30 min intervals were given to all participants. All $ETCO_2$ values measured after each time of breathing were recorded from different capnometers. All capnometers were calibrated regularly each time before initiating breathing tests of individual participant. The flow sampling rate in microstream capnometer was 50 ml/min. Sampling lines and adapters installed on capnometers were also changed accordingly (Figure 2).

The primary endpoint is the comparison of $ETCO_2$ values measured in water exposing conditions by pDCCM and dDCCM in both mainstream and microstream settings. The secondary endpoint is the reliability of $ETCO_2$ values measured by dDCCM among three different water conditions in both mainstream and microstream settings.

2.3. Equipment. Two types of portable capnometers were used in this study: (1) EMMA™ Mainstream Capnometer (Masimo Corp., CA, US) equipped on to EMMA airway adapter, which operates at -5 to 50°C temperature with 10-95% humidity [10]; and (2) Microcap® Plus Microstream Capnography (Oridion Medical Ltd., Jerusalem, Israel) connected to Smart CapnoLine Plus sampling line (Oridion Medical Ltd., Jerusalem, Israel) [11]. By detecting infrared absorption, both capnometers can measure $ETCO_2$ within the range of 0-99 mmHg. Direct connect catheter mount (DCCM) is at the length of ~15 cm with mechanical dead space equivalent to 25 ml. The ETT (Mallinckrodt™ Hi-Lo Oral/Nasal Tracheal Tube Cuffed Murphy Eye, Covidien, MA, USA) utilized was 7.5 size with 15 ml mechanical dead space [12].

2.4. Statistical Analysis. Prior to the experiments, minimum sample size was calculated based on our pilot study results. Briefly, when ETT was sprayed with 5 ml water, mean $ETCO_2$ values measured by pDCCM and dDCCM were 14.4 ± 19.9 mmHg and 29.2 ± 7.4 mmHg, respectively. Difference from dDCCM to pDCCM was 14.7 ± 20.6 mmHg. Sample size was calculated by Wilcoxon-signed rank test using G-power software (version 3.1.7; Heine Heinrich University, Düsseldorf, Germany). By using $\alpha = 0.05$ and $\beta = 0.05$, it was concluded that at least 21 participants are required.

SPSS software (version 20; IBM Corp, NY, USA) was used for data analysis. All variables were analyzed with Shapiro-Wilk normality test. $ETCO_2$ values measured in water sprayed conditions were analyzed by repeated measures ANOVA. The graphs showing individual $ETCO_2$ values monitored from every breath over time were represented as mean with standard errors (95% CI) using error bars. We analyzed the agreement of ETCO2 measurement between pDCCM and dDCCM using Bland-Altman plots. We also compared the agreement of ETCO2 measurement between mainstream and microstream capnometer. The intraclass

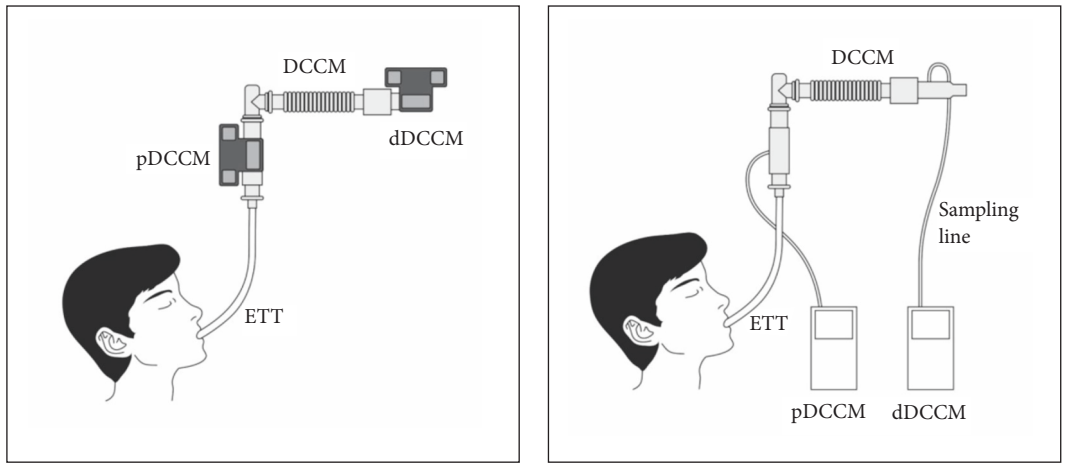

Figure 1: *Schematic figures of (a) mainstream capnometers and (b) microstream capnometers.* Abbreviations: DCCM, direct connect catheter mount; dDCCM, distal capnometer of direct connect catheter mount; ETT, endotracheal tube; pDCCM, proximal capnometer of direct connect catheter mount.

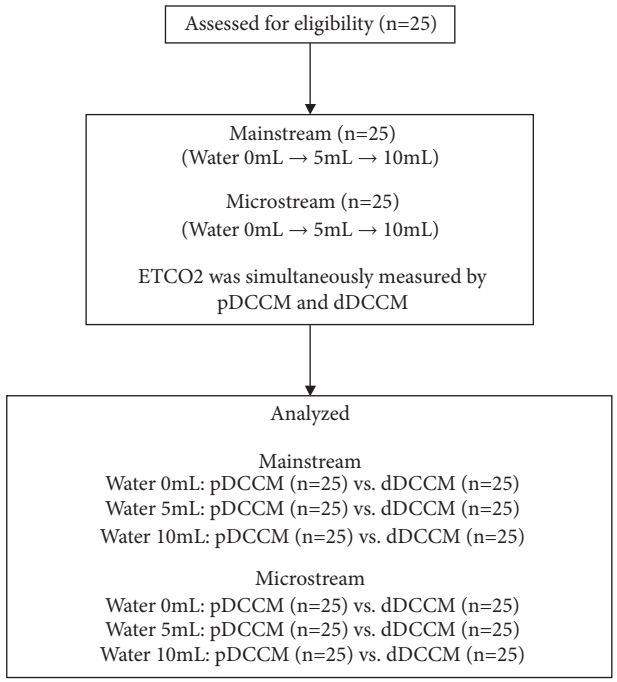

Figure 2: *Flow chart of experimental groups.* Abbreviations: dDCCM, distal capnometer of direct connect catheter mount; $ETCO_2$, End-tidal carbon dioxide; pDCCM, proximal capnometer of direct connect catheter mount.

correlation coefficient (ICC) was calculated for $ETCO_2$ values of dDCCM to estimate interrater reliability among three different water conditions. All data are shown as means ± SD. p-value < 0.05 was considered significant.

3. Results

3.1. Overall $ETCO_2$ Measured by pDCCM and dDCCM. Table 1 shows the overall characteristics of the 25 participants, and Table 2 shows overall $ETCO_2$ measured by pDCCM and dDCCM. For both mainstream and microstream capnometers, $ETCO_2$ values measured by pDCCM and dDCCM were compared under three different water conditions (0, 5, or 10 ml water sprays) (Table 2). For mainstream capnometers, $ETCO_2$ measurements at baseline did not show statistically significant differences ($p = 0.09$) between pDCCM (34.5 ± 6.5 mmHg) and dDCCM (31.9± 4.9 mmHg). However, when 5 and/or 10 ml water sprays were given to the ETT, $ETCO_2$ measurement was significantly ($p < 0.001$) higher in dDCCM than in pDCCM (29.5 ± 7.0 mmHg vs. 19.0 ± 23.5 mmHg with 5 ml water; 33.8 ± 14.8 mmHg vs. 21.2 ± 24.5 mmHg for 10 ml water). Likewise, for microstream capnometers, $ETCO_2$ measurements at a baseline were similar ($p = 0.83$) between pDCCM (32.5 ± 3.7 mmHg) and dDCCM (32.7 ± 4.3 mmHg), whereas with 5 and/or 10 ml water sprays, $ETCO_2$ measurement was greatly ($p < 0.001$) higher in dDCCM than in pDCCM (30.5 ± 5.1 mmHg vs. 13.9 ± 15.2 mmHg with 5 ml water; 29.9 ± 4.3 mmHg vs.11.4 ± 14.4 mmHg with 10 mL water). These results indicate that the use of DCCM can reduce capnometer malfunctioning under water exposing conditions.

3.2. Individual $ETCO_2$ for Each Breath Measured by pDCCM and dDCCM. Individual $ETCO_2$ values for each breath over time measured by pDCCM and dDCCM are shown in Figure 3. For both mainstream and microstream capnometers when treated with 5 and/or 10 ml water sprays, $ETCO_2$ measurements by pDCCM were far lesser than those at baseline (0 ml water), whereas these measurements by dDCCM were very close to those at baseline. In the Bland-Altman plot, wider range of the 95% limits of agreement was shown in the water exposing conditions (5, 10mL in ETT) comparing with baseline (0mL in ETT) for both capnometers, which suggests inaccuracy of pDCCM under water exposing conditions [13]. Additionally, the microstream capnometer showed better

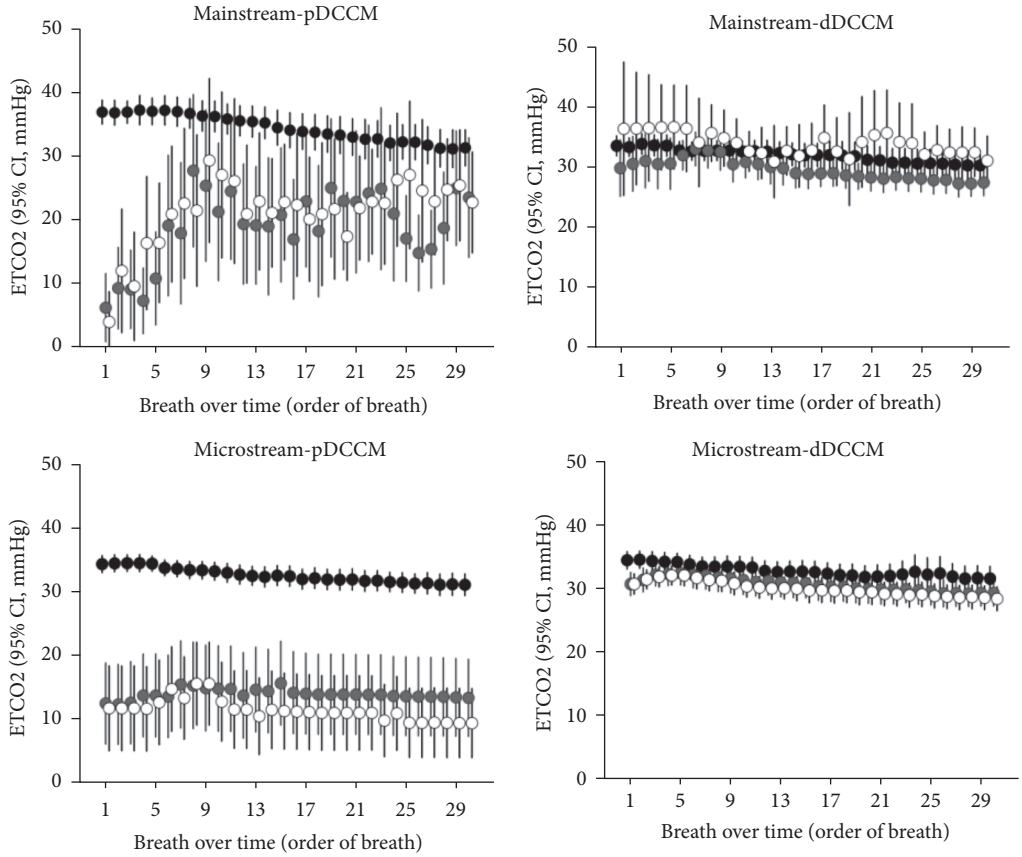

Figure 3: *Individual $ETCO_2$ for each breath over time measured by pDCCM and dDCCM under different water conditions (black circle - no water, grey circle - 5 ml water, white circle - 10 ml water) created within the endotracheal tube*. Individual ETCO2 values monitored from every breath over time were represented as mean with standard errors (95% CI) using error bars. Abbreviations: dDCCM, distal capnometer of direct connect catheter mount; $ETCO_2$, End-tidal carbon dioxide; pDCCM, proximal capnometer of direct connect catheter mount.

agreement between pDCCM and dDCCM than mainstream capnometer (Supplementatary Figure S1).

3.3. Reliability of $ETCO_2$ Measured by dDCCM. For both mainstream and microstream capnometers, the reliability of $ETCO_2$ measured by dDCCM was assessed among three different water conditions (0, 5, or 10 ml water sprays). When using mainstream settings, $ETCO_2$ measured by dDCCM was unreliable (average measure ICC 0.27, 95% CI 0.17-0.35; $p < 0.001$). On the contrary, $ETCO_2$ measured by dDCCM was reliable in microstream settings (average measure ICC 0.88, 95% CI 0.87-0.89; $p < 0.001$) among three different water conditions. In the analysis using Bland-Altman plot, dDCCM showed better agreement between microstream and mainstream capnometer than pDCCM (Supplementatary Figure S2).

4. Discussion

This is a concept study that simulates fluid using water and evaluates the efficacy of DCCM in yielding reliable $ETCO_2$ under fluid exposing conditions. The key finding from this study is that adoption of DCCM can reduce capnometer malfunctioning particularly when fluid inflow occurs through the ETT. It was evident from the results that, under water exposing conditions (5 or 10 ml water sprays), $ETCO_2$ measurements were significantly lower in pDCCM than in dDCCM in both mainstream and microstream capnometers. With water, additionally, all $ETCO_2$ values measured by pDCCM were far less than baseline $ETCO_2$ (0 ml water spray), indicating that these levels of water caused pDCCM malfunctioning. On the contrary, $ETCO_2$ values obtained from dDCCM placing away from water sources were very similar to the baseline $ETCO_2$, implying that securing some distance from patients (~15 cm) [9] by DCCM installation seems to be effective in protecting against capnometer malfunctioning by lessening water vapor concentrations and inhibiting the capnometers from direct water contact.

We did not set partial pressure of carbon dioxide ($PaCO_2$) in arterial blood gas analysis as a reference standard. Since there could be wide gap between $ETCO_2$ and $PaCO_2$ under water exposing conditions, baseline $ETCO_2$ (0 ml water spray) was set to the reference standard.

$ETCO_2$ monitoring is most reliable and accurate method to monitor success for tracheal intubation or CPR quality. However, under fluid exposing conditions, fluid could hinder obtaining reliable $ETCO_2$ in proximal ETT. Additionally, in

Table 1: General characteristics.

Characteristics	Data (n=25)
Age (yr)	30.6 ± 4.2
Male sex	19 (76)
Height (cm)	170.7 ± 7.4
Weight (kg)	69.5 ± 11.9
∗IBW (kg)	65.5 ± 8.4
†BSA (m^2)	1.8 ± 0.1
‡Predicted tidal volume ($ml \cdot kg^{-1}$)	458.8 ± 58.3
BMI ($kg \cdot m^{-2}$)	23.6 ± 2.6
Underlying lung disease	None
Carbohydrate beverage ingestion before study	None

Categorical variables are given as numbers (percentage). Continuous variables are given as mean ± SD.

∗ Calculated by Devine formula; IBW (male) = 50 + 2.3 x (height over 60 inches); IBW (female) = 45.5 + 2.3 x (height over 60 inches)

† Calculated by Mosteller formula; BSA (m^2) = (Height (cm) x Weight (kg) / 3600)$^{1/2}$

‡ Calculated by the formula for tidal volume in health young adults; 7 (ml) x IBW (kg)

Abbreviations: BMI, body mass index; BSA, body surface area; IBW, ideal body weight; SD, standard deviation

cases of patients receiving CPR or having fluid, low $ETCO_2$ could be frequently observed. This study suggests that the use of DCCM could provide benefit to obtain more reliable $ETCO_2$ by using DCCM in those cases.

It is of interest that, under water exposing conditions, the use of DCCM was more effective in microstream capnometer than in mainstream capnometer. It could be explained by the fact that the infrared sensor of mainstream capnometer was directly exposed to water, being vulnerable to being malfunctioning, whereas that of microstream capnometer was indirectly exposed to water via sampling lines connected to the opposite direction of gravity, implying that a continuous measurement of $ETCO_2$ is possible unless there is water condensation and/or direct water contact.

In this study, two types (mainstream vs. microstream) of capnometers were used for CO_2 monitoring. Depending on the use of gas sampling system, capnometers can be classified into two categories such as mainstream capnometer and sidestream capnography [1, 14], and the microstream capnograph used in this study is a type of sidestream capnography [14]. Mainstream capnometer can measure $ETCO_2$ directly by using infrared sensor and does not need gas sampling system [1, 3]. Both the sidestream and microstream capnographs can monitor CO_2 aspirated by sampling line [1, 3]. Water vapor can cause condensation in sample lines which can thus interfere with CO_2 monitoring [1]. The occurrence of capnometer malfunctioning caused by water condensation is more often in sidestream capnograph compared to microstream capnograph. It is also known that, compared to mainstream capnometer, sidestream capnograph is more vulnerable to water itself [3]. It is the reason why mainstream capnometer and microstream capnograph were chosen for this study in assessing the level of capnometer malfunctioning under water exposing conditions.

This study was performed under water exposing conditions, where two different water conditions were simulated by spraying 5 ml or 10 ml of distilled water into ETT. These water amounts were equivalent to one-third (5 ml) or two-thirds (10 ml) of mechanical dead space of tracheal tube (15 ml), which was gauged by filling water into the tracheal tube.

From the study, we found that, in water exposing conditions, measuring $ETCO_2$ is more accurate when using DCCM. In spite of it, using dDCCM to monitor $ETCO_2$ is not the way traditionally recommended. Earlier studies indicated that $ETCO_2$ measurement should be performed at the proximal point of tracheal tube (pDCCM) connected to the ventilator circuit [15], in order to avoid possible inconsistency between $PaCO_2$ and $ETCO_2$ when measured by dDCCM. We found that a baseline $ETCO_2$ value for mainstream capnometers was significantly lower in dDCCM than in pDCCM. However, when measured by microstream, mean $ETCO_2$ values were not significantly different between pDCCM and dDCCM. We assume that it is originated from the difference of gas sampling technique in capnometer. A microstream capnometer withdraws a continuous sample of gas through a capillary tube from the patient's airway to the monitor and a water trap removes particles of water before measurement takes place. Hence, dDCCM of mainstream capnometer is more vulnerable to water vapor than microstream.

This study has several limitations. Firstly, use of DCCM might not guarantee the complete inhibition of capnometer malfunctioning during water exposing conditions, as installation of DCCM itself is not sufficient to block water contact completely, but rather it can help in reducing the capnometer malfunctioning by allowing a certain distance from the water sources. Secondly, in simulating fluid, pure water was used in this study to prevent ethical conflicts in healthy volunteers. The potential effect of other components of fluid on the infrared sensor of capnometer remains still unknown. Thirdly, when conducting this study, other resuscitation techniques (i.e., suctioning and bag valve mask ventilation) were excluded, as they can act as confounding factors when analyzing the sole effect of DCCM on capnometer malfunctioning. Fourthly, the CO_2 rebreathing effect possibly occurring during DCCM mounting onto the ETT was incompletely corrected. As 25 ml dead space of DCCM can increase the CO_2 rebreathing effect and elevate baseline $ETCO_2$ for both pDCCM and dDCCM, a possible gap still exists between $ETCO_2$ measurements obtained from this study and real CO_2 levels from exhales of the participants. However, to avoid rebreathing effect, participants were guided to exhale forcefully to reach maximal flow rate and tidal volume.

5. Conclusions

In conclusion, application of DCCM onto the capnometer setting seems to be effective in reducing capnometer malfunctioning under fluid exposing conditions, which is obvious in microstream capnometer by producing more reliable $ETCO_2$. To demonstrate the efficacy of DCCM in real world patients under fluid exposing conditions, further clinical studies are needed.

Table 2: $ETCO_2$ by using pDCCM and dDCCM.

Capnometer	Water sprays	∗$ETCO_2$ (mmHg) †pDCCM (n=25)	‡dDCCM (n=25)	Mean difference	§p-value
Mainstream	0 ml	34.5 ± 6.5	31.9 ± 4.9	-2.5 ± 5.2	0.09
	5 ml	19.0 ± 23.5	29.5 ± 7.0	10.4 ± 24.1	<0.001
	10 ml	21.2 ± 24.5	33.8 ± 14.8	12.5 ± 28.4	<0.001
Microstream	0 ml	32.5 ± 3.7	32.7 ± 4.3	0.2 ± 2.5	0.83
	5 ml	13.9 ± 15.2	30.5 ± 5.1	16.6 ± 16.7	<0.001
	10 ml	11.4 ± 14.4	29.9 ± 4.3	18.5 ± 16.0	<0.001

∗ Values are given as mean ± SD.
†pDCCM, proximal capnometer of direct connect catheter mount
‡dDCCM, distal capnometer of direct connect catheter mount
§Calculated by repeated measures ANOVA.
Abbreviations: dDCCM, distal capnometer of direct connect catheter mount; $ETCO_2$, End-tidal carbon dioxide; pDCCM, proximal capnometer of direct connect catheter mount; SD, standard deviation

Data Availability

All data and materials in this study are fully available without restriction.

Conflicts of Interest

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

Authors' Contributions

Literature search was performed by W. Kim, H. J. Choi, and J. Oh. Data collection was done by W. Kim and Y. Cho; W. Kim, H. J. Choi, T. H. Lim, and B. S. Kang performed study design. Analysis of data was done by W. Kim, Y. Cho, and I. Y. Kim; Y. Cho, W. Kim, Y. Kim, T. H. Lim, and B. S. Kang were responsible for manuscript preparation. And review of manuscript was performed by Y. Cho, W. Kim, Y. Kim, T. H. Lim, I. Y. Kim, and J. Oh.

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Supplementary Materials

Figure S1. Bland-Altman plots for evaluating agreement of ETCO2 measurement between pDCCM and dDCCM under water exposing conditions (baseline, 5 mL water, 10 mL water). Figure S2. Bland-Altman plots for evaluating agreement of ETCO2 measurement between mainstream and microstream capnometer under water exposing conditions (baseline, 5 mL water, and 10 mL water). *(Supplementary Materials)*

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