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The future of resuscitation

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INTRODUCTION

The estimated annual incidence of emergency medical service (EMS)-treated out-of-hospital cardiac arrest (OHCA) is 30.0 to 97.1 patients per 100,000 population and this will increase with population aging [1,2]. Although cardiopulmonary resuscitation (CPR) guidelines have been updated based on scientific evidence and implemented in clinical practice, no major breakthroughs have been made to improve the survival rate or neurological recovery of cardiac arrest patients [2–4]. Recently, various trials have been attempted in the field of resuscitation with technological advances and system development. This commentary seeks to introduce the future of resuscitation in terms of cardiac arrest treatment and resuscitation science.

NEW TOOLS FOR CARDIAC ARREST RECOGNITION AND EMS ACTIVATION

Wearable devices can obtain varied personalized health data such as blood pressure, oximetry, electrocardiography, or electroencephalography [5]. Despite concerns about the safety and reliability of using wearable devices in healthcare, these “little uncomfortable monitoring systems” can be used to detect early warning signs of sudden cardiac death. Passive agonal breathing detection software using a smartphone speaker has shown high accuracy for detecting and differentiating hypopnea, central apnea, or obstructive apnea [6]. A machine learning-based dispatcher recognition of OHCA demonstrated the potential to surpass human recognition in a randomized clinical trial [7]. A mobile application (app) has been designed to identify prodromal symptoms in patients who are at highest risk for acute cardiac events including acute myocardial infarction or sudden cardiac death (SCD). This system can alert an individual and EMS simultaneously [8]. A single depth camera detecting thoracic and abdominal respiration can be a tool for detecting unanticipated emergencies in a medical facility with insufficient monitoring systems [9]. This technology can be applied to the detection of cardiac arrest in residential care settings.

INCREASING Bystander CPR WITH A MOBILE PHONE-BASED ALERT SYSTEM

During the treatment of cardiac arrest, CPR and/or automated external defibrillator (AED) use by a bystander has a crucial impact on resuscitation outcomes. A mobile phone can be a medium for alerting potential rescuers to a nearby cardiac arrest. The arrival of citizen responders dispatched by an app or short message system (SMS) before the arrival of EMS is associated with a high rate of bystander CPR and an increase in bystander defibrillation rate resulting in favorable re-
FACILITATING ACCESS TO PUBLIC AEDs

Early defibrillation is a key treatment for victims with a shockable rhythm [13]. Dispatching citizen responders using an app or SMS increases AED use and improves resuscitation outcomes [10,11]. Inadequate maintenance of public AEDs and limited 24-hour availability are significant issues limiting the effectiveness of public access defibrillation (PAD) programs in the community [14]. The 24-hour accessibility is limited for AEDs installed in places that are not open 24 hours. Whether the installation site is open 24 hours should be considered when planning a PAD program. Installation of AEDs on walls outside of buildings is one way to facilitate access to AEDs. The delivery of AEDs to the scene of cardiac arrest by drones is emerging as a new way to increase on-site defibrillation. Delivery of an AED by drones shortens total time from cardiac arrest to AED use compared to ground search for an AED [15]. An autonomous drone AED system activated by trained citizen responders is feasible and makes it possible to perform defibrillation before EMS arrival [16]. Integration of an automatic chest compression device and an AED as an all-in-one CPR device may shorten the time from collapse to chest compression and defibrillation, which could increase survival and improve neurologic outcomes in OHCA patients.

OPTIMIZING PERFUSION DURING CPR

Physiology-directed CPR results in better resuscitation outcome than advanced life support conforming to the current CPR guidelines [17,18]. However, since hemodynamic measurements can only be performed in hospitals equipped with invasive monitoring equipment, there are limitations in the general application of physiology-directed CPR. Development of technologies for waveform analysis of chest compression and prediction of hemodynamic parameters will make it possible to guide high-quality, physiology-directed CPR during prehospital resuscitation [19,20]. Prehospital application of extracorporeal CPR can be used to optimize perfusion in OHCA patients as extracorporeal membrane oxygenators are becoming more compact and easier to apply to patients [21].

REINFORCING THE SURVIVAL ENVIRONMENT FOR CARDIAC ARREST

The survival environment for cardiac arrest includes medical and nonmedical factors related to the prevention, treatment, and rehabilitation of victims of cardiac arrest [13]. Technological advances in medical and nonmedical aspects will reinforce the survival environment of cardiac arrest in the future. For example, widespread use of social media will increase public awareness of cardiac arrest and CPR, improve CPR education, and thus raise the rate of bystander CPR and early defibrillation.

Primary prevention of SCD is the best way to prevent the consequences arising in the event of cardiac arrest. Recent studies investigating risk factors for SCD suggest that healthy lifestyle modifications are associated with low odds of SCD occurrence [22–24]. Machine learning-based analysis of large population-based clinical data and omics technology using minimal blood samples have attracted attention in terms of SCD risk factor analysis [25,26]. These new technologies can predict the risk of SCD, not only in the individual but also in the population, which can be applied to establishing regional and national healthcare policies to reduce SCD.

Changes in the community can affect the survival environment for cardiac arrest. The COVID-19 pandemic forced us to shift the methods of CPR education from group-based simulation to self-training with or without virtual-reality or blended learning [27–29]. The technological developments in CPR education triggered by the COVID-19 pandemic may contribute to improving accessibility and implementation of CPR education.

Regional variation in cardiac arrest survival is a growing issue in resuscitation science [1]. Standardization and regionalization of the survival environment for cardiac arrest should be implemented globally by creating standardized registries and applying the results from these registries to policies to improve cardiac arrest survival.

CONCLUSION

New technologies such as wearable devices, mobile phones and apps, remote monitoring devices, social media, drones, and hemodynamic CPR feedback devices will contribute to improved cardiac arrest survival in several ways, including early detection of cardiac arrest, promotion of public awareness of cardiac arrest and wider availability of CPR education, early CPR and defibrillation, and optimization of perfusion in the near future. Solutions to reinforcing the survival environment for cardiac arrest should be developed by creating global registries, identifying populations at high risk for cardiac arrest, and establishing effective cardiac arrest treatment systems.
CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conceptualization: KCC; Data curation: KCC; Visualization: all authors; Writing–original draft: KCC; Writing–review & editing: SOH. All authors read and approved the final manuscript.

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Targeted temperature management with hypothermia for comatose patients after cardiac arrest

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Targeted temperature management with mild hypothermia (TTM-hypothermia; 32–34 °C) is a treatment strategy for adult patients who are comatose after cardiac arrest. Robust preclinical data support the beneficial effects of hypothermia beginning within 4 hours of reperfusion and maintained during the several days of postreperfusion brain dysregulation. TTM-hypothermia increased survival and functional recovery after adult cardiac arrest in several trials and in real-world implementation studies. TTM-hypothermia also benefits neonates with hypoxic-ischemic brain injury. However, larger and methodologically more rigorous adult trials do not detect benefit. Reasons for inconsistency of adult trials include the difficulty delivering differential treatment between randomized groups within 4 hours and the use of shorter durations of treatment. Furthermore, adult trials enrolled populations that vary in illness severity and brain injury, with individual trials enriched for higher or lower illness severity. There are interactions between illness severity and treatment effect. Current data indicate that TTM-hypothermia implemented quickly for adult patients after cardiac arrest, may benefit select patients at risk of severe brain injury but not benefit other patients. More data are needed on how to identify treatment-responsive patients and on how to titrate the timing and duration of TTM-hypothermia.

Keywords Heart arrest; Coma; Hypothermia; Resuscitation; Brain

What is already known
Many guidelines recommend targeted temperature management with hypothermia for patients who are comatose after cardiac arrest, but recent large clinical trials could not detect benefits from hypothermia.

What is new in the current study
This review summarizes how hypothermia when implemented quickly during or after reperfusion treats specific pathophysiology that may be present in some patients after cardiac arrest. Patients enrolled in clinical trials vary in severity, and many patients may not have hypothermia-sensitive pathology. Observational data suggest hypothermia might benefit subgroups of patients who can be identified with clinical exam, imaging, or electroencephalography.
INTRODUCTION

For a patient who is comatose after cardiac arrest, clinicians must immediately decide whether or not to manipulate temperature and whether to specifically target a lower-than-normal body temperature. Targeted temperature management with mild hypothermia (TTM-hypothermia) is a strategy in which treatment includes lowering the patient core temperature to 32 to 34 °C for a period of time, typically 24 hours in adults. The use of TTM-hypothermia has been supported by international guidelines since 2003 [1–4]. There is extensive preclinical data supporting the biological plausibility of a beneficial effect of TTM-hypothermia [5,6]. Multiple systematic reviews have summarized the clinical evidence for using TTM-hypothermia versus normothermia in cardiac arrest [7,8]. This review synthesizes the current understanding of TTM-hypothermia as a tool for treating adult cardiac arrest. First, laboratory data describe that the effective therapeutic window for TTM-hypothermia probably is within 4 hours of return of spontaneous circulation (ROSC), with declining benefit later. Second, many plausible physiological mechanisms may mediate beneficial effects of TTM-hypothermia on neurological recovery, but few cardiac arrest trials measure these mediators. Third, some clinical studies in adults, children, and neonates support use of TTM-hypothermia in certain populations. Fourth, larger clinical trials in more heterogeneous populations fail to detect any benefit from TTM-hypothermia, though all trials based on current practice barely achieve differential treatment of groups within 4 hours. Fifth, clinical studies suggest that TTM-hypothermia might have benefit for selected adult patients even if there is no detectable benefit for heterogeneous groups of patients. Future clinical research must consider whether TTM-hypothermia is implemented within the therapeutic window and whether the enrolled patient population includes individuals likely to benefit from TTM-hypothermia.

PRECLINICAL DATA ON TIMING FOR TTM-HYPOTHERMIA

It is well-established that lowering the temperature of the brain as much as possible prior to ischemia will protect the brain from injury (Fig. 1) [8]. By reducing metabolic rate, this protective hypothermia reduces demand for oxygen and substrate thereby prolonging tolerance to interruption in supply [9]. However, protective hypothermia is only practical in clinical situations where ischemia is anticipated, such as during surgery requiring circulatory arrest [10]. Protective hypothermia is clinically relevant for treating adult cardiac arrest patients who may have been hypothermic prior to cardiac arrest: these patients have much higher chance of survival and recovery even after prolonged cardiac arrest [11].

Induced mild hypothermia (32 to 35 °C) after ischemia also reduces final brain injury after global ischemia in multiple animal species (Fig. 1) [5,6]. Unlike protective hypothermia, deleterious effects of postischemia hypothermia increase for temperatures less than 30 °C without any additional neurological benefit [12]. Hypothermia should begin as soon as possible during or after reperfusion [13,14].

Postischemia hypothermia treatment has two targets with two different therapeutic windows: (1) reducing the immediate reperfusion injury and (2) reducing secondary brain injury (Fig. 1). Treating reperfusion injury requires hypothermia immediately within

![Diagram](image-url)

**Fig. 1.** Targeted temperature management with mild hypothermia can benefit ischemic brain injury in different ways, depending on when it is delivered. Specifically, hypothermia can protect from brain injury, reduce reperfusion injury, or treat secondary brain injury. CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation.
minutes during the reperfusion of previously ischemic brain and is effective even if the duration of hypothermia is brief [13–15]. Even 1 hour of TTM-hypothermia improves brain recovery, but delays longer than 15 minutes [13] or 20 minutes [14] after ROSC reduce any benefit. Furthermore, initiating hypothermia after 20 minutes of cardiopulmonary resuscitation (CPR) is less effective than after 10 minutes of CPR [15]. Hypothermia to treat reperfusion injury has prompted clinical studies of intra-arrest cooling. While rapid reductions in temperature are possible in small animals, technical challenges remain for delivering this intervention to patients [16–18].

Treating secondary brain injury requires manipulation of temperature over the hours and days after reperfusion when the brain is vulnerable. Too brief hypothermia (<5 hours) does not afford any detectable benefit [19,20] and durable benefit after global brain ischemia or hypoxia may require 48 hours or more of treatment [21,22].

Beneficial effects of prolonged TTM-hypothermia on behavioral outcomes and survival are reliable when hypothermia starts within 4 hours after reperfusion but not when treatments differ at 8 hours after reperfusion (Fig. 2) [19,23]. Likewise, histological signs of brain damage are reduced in all brain areas when TTM-hypothermia groups have different temperatures by 2 hours after reperfusion but not in the striatum when TTM-hypothermia is delayed for 6 hours nor in parts of the hippocampus when delayed for 12 hours [19,23]. Because this time window for initiating treatment is more easily achieved in adult humans, most clinical research has focused on TTM-hypothermia for treating secondary brain injury after cardiac arrest [24–29].

Thus, under ideal laboratory conditions with tight control over other treatments and with homogenous injury severities, TTM-hypothermia reliably reduces brain injury when experimental groups have different temperatures by 4 hours or less after reperfusion, and benefits increase with durations of TTM-hypothermia beyond 24 hours.

**POTENTIAL MECHANISMS FOR BENEFICIAL EFFECTS OF TTM-HYPOTHERMIA**

Experimental data do not identify a single mechanism mediating the beneficial effects of TTM-hypothermia on secondary brain injury. Temperature affects multiple pathophysiological processes that might influence brain recovery. Hypothermia attenuates many processes that are associated with brain injury but also stimulates other reparative processes. Experimental studies rarely determine whether or not these associated pathophysiological changes are in the causal pathway for the beneficial effects of lower temperature. Examples of pathophysiological processes that are influenced by temperature manipulation include seizures, brain edema, metabolic rate, and molecular processes.

Seizures and nonconvulsive status epilepticus occur frequently after cardiac arrest and are associated with worse outcomes [30,31]. Temperature is positively correlated with seizure frequency in animal models [32,33] and fever or increased temperature is a well-known trigger of seizures in humans [34]. Based on these observations, hypothermia has been used to treat refractory seizures, though supporting clinical evidence is compromised by mostly uncontrolled case series [35]. In a controlled clinical trial for patients with refractory seizures not resulting from cardiac arrest, TTM-hypothermia did reduce seizure duration and progression to persistent electroencephalography (EEG)-confirmed status epilepticus by 6 to 12 hours [36]. Induced hypothermia does reduce epileptiform discharges in posthypoxic sheep [37].

Cerebral edema and intracranial hypertension occur over the
Several clinical trials support the use of TTM-hypothermia for adult cardiac arrest [24,25,62]. In one trial, 275 out-of-hospital cardiac arrest (OHCA) patients were assigned to TTM-hypothermia (32–34 °C, n = 137) or usual temperature care (n = 138) for 24 hours, followed by passive rewarming over approximately 8 hours [24]. TTM was initiated at a median of 105 minutes after ROSC, and temperatures differed between groups by 4 hours after ROSC. Patients reached target temperature a median of 8 hours (interquartile range [IQR], 4–16 hours) after ROSC. TTM-hypothermia patients had higher survival (59% vs. 45%) and favorable functional status at hospital discharge (55% vs. 39%).

The second trial assigned 77 OHCA patients to TTM-hypothermia (33 °C, n = 43) or usual care (n = 34) for 12 hours followed by rewarming over 6 hours (0.7 °C/hr) [25]. In this trial, temperatures differed between groups by 120 minutes after ROSC, and TTM-hypothermia patients had a mean temperature 33.3 °C by the time of intensive care unit (ICU) admission. TTM-hypothermia patients had higher survival (49% vs. 32%) and normal-minimal disability at hospital discharge (35% vs. 21%).

Both of these trials focused on very select patients with OHCA that included shockable cardiac rhythms. This is a population with a more favorable prognosis compared to the entire population of cardiac arrest patients but represented only about 8% of all screened patients in one trial [24]. In addition, both trials compared TTM-hypothermia to usual care, and usual care permitted fever for logistical reasons, did not regiment decisions on withdrawal of life sustaining treatments (WLST), and may have had other unmeasured sources of bias. These methodological limitations, along with the relatively small total number of patients randomized, raised concerns about the reproducibility of the findings [63].

The more recent HYPERION (Therapeutic Hypothermia after Cardiac Arrest in Nonshockable Rhythm) trial specifically examined the treatment effect for TTM-hypothermia in patients after either OHCA or in–hospital cardiac arrest (IHCA) with nonshockable rhythms [62]. Investigators randomly assigned 584 patients to TTM-hypothermia (33 °C) or normothermia (36.5–37.5 °C) for 24 hours followed by rewarming at 0.25 to 0.5 °C/hr. Median time from ROSC to randomization for TTM-hypothermia was 232.5 minutes (IQR, 178–276.5 minutes). The goal of 33 ± 0.5 °C was obtained a median of 317 minutes (IQR, 214–477 minutes) after randomization. TTM-hypothermia patients had higher rates of favorable functional recovery (10.2% vs. 5.7%), though survival was not reliably different (19.7% vs. 16.8%).

One trial compared 24 hours versus 48 hours of TTM-hypothermia in adult OHCA. This trial randomly assigned 351 patients resuscitated from OHCA to 24 hours (n = 176) or 48 hours (n = 175) of TTM-hypothermia (33 °C), followed by rewarming at 0.5 °C/hr
[29]. Target temperature was achieved a median of 281 minutes (IQR, 217–360 minutes) after ROSC for the 48-hour group and 320 minutes (IQR, 241–404 minutes) after ROSC for the 24-hour group. Favorable functional recovery (69% vs. 64%) and survival (73% vs. 66%) at 6 months were numerically higher for the 48-hour group but differed less than the 15% absolute difference the trial could detect.

ADULT TRIALS DETECTING NO BENEFIT FROM TTM–HYPOTHERMIA

Subsequent clinical trials in adults improved many methodological flaws in the original studies supporting TTM-hypothermia. Particular attention was placed on rigorous randomization, obtaining a complete larger multicenter cohort, and regimenting decisions about WLST.

In the TTM Trial, 939 OHCA patients were randomly assigned to TTM-hypothermia (33 °C, n = 473) or near-normal temperature control (TTM–36 °C; n = 466) for 28 hours, followed by controlled rewarming at 0.5 °C/hr [26]. Temperatures differed between groups by 3 to 5 hours after randomization, but randomization was allowed up to 4 hours after ROSC. The time from ROSC until groups differed in temperature treatment is not clear. WLST was discouraged prior to 72 hours, and prognostic assessments were provided after 72 hours by a clinician blinded to treatment and using established criteria. TTM-hypothermia and TTM–36 °C patients had similar survival (50% vs. 52%) and good functional recovery at 180 days (46% vs. 48%).

In the TTM2 Trial, 1,861 OHCA patients were randomly assigned to TTM-hypothermia (33 °C, n = 930) or to active fever prevention (n = 931) for 28 hours, followed by controlled rewarming at 0.5 °C/hr [27]. Median time from ROSC until randomization was 136 minutes (IQR, 103–170 minutes) for TTM-hypothermia, and this group reached ≤ 34 °C at a median of 3 hours after randomization. Temperatures in treatment groups were separated by 4 to 5 hours after randomization. Again, WLST was regimented and measured. TTM-hypothermia and fever prevention patients had similar survival at 6 months (50% vs. 52%) and good functional recovery at 180 days (45% vs. 45%).

In a trial examining hypothermia for IHCA patients, 242 patients were randomly assigned to TTM-hypothermia (n = 123) or normothermia (n = 119) for 24 hours followed by controlled rewarming at 0.25 °C/hr [28]. Mean ± standard deviation time from randomization to a temperature < 34 °C was 4.2 ± 2.8 hours, with mean ± standard deviation time from arrest to intervention of 2.2 ± 1.3 hours. Temperatures were separated by 3 to 4 hours after beginning the intervention. TTM-hypothermia patients had similar 6-month survival (27% vs. 29%) and favorable functional recovery (23% vs. 24%).

A few questions remain about these trials. First, was the intervention applied quickly enough? TTM-hypothermia used in the recent trials represented contemporary clinical practice in Europe, but many patients had TTM regimens selected upon ICU admission rather than during initial emergency care [26–28]. Thus, treatment groups may not have had robustly different temperatures for 5 to 6 hours after ROSC. This is longer than the 4 hours therapeutic window for efficacy of hypothermia in animal studies [19,23] and longer than the delay in the original efficacy trials

Table 1. Features of patients and time of intervention in clinical trials

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<tr>
<td>Shockable rhythm (%)</td>
<td>96</td>
<td>79</td>
<td>74</td>
<td>0</td>
<td>24</td>
</tr>
<tr>
<td>Initial lactate (mmol/L)</td>
<td>-</td>
<td>6.7 ± 4.5</td>
<td>5.9 ± 4.4</td>
<td>5.8 (3.2–9)</td>
<td>6.3 ± 5.7</td>
</tr>
<tr>
<td>Pupillary reflex present (%)</td>
<td>-</td>
<td>77</td>
<td>69</td>
<td>42</td>
<td>-</td>
</tr>
<tr>
<td>Shock present (%)</td>
<td>52</td>
<td>14</td>
<td>29</td>
<td>58</td>
<td>-</td>
</tr>
<tr>
<td>Overall survival (%)</td>
<td>52</td>
<td>51</td>
<td>51</td>
<td>18</td>
<td>28</td>
</tr>
<tr>
<td>ROSC to randomization (min)</td>
<td>120</td>
<td>-</td>
<td>136 (103–170)</td>
<td>232.5 (178.0–276.5)</td>
<td>132 ± 78</td>
</tr>
<tr>
<td>Randomization to T ≤ 34 °C (hr)</td>
<td>8 (4–16)</td>
<td>3–4</td>
<td>3</td>
<td>5.3 (3.8–8.0)</td>
<td>4.2 ± 2.8</td>
</tr>
<tr>
<td>Group mean or median (hr)</td>
<td>4°</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>3</td>
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<tr>
<td>Differ by 1 °C</td>
<td>5°</td>
<td>3</td>
<td>5</td>
<td>4</td>
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Values are presented as number, mean ± standard deviation, or median (interquartile range). Data for overall population. Populations enrolled in adult clinical trials differ in proportions with shock, impaired brainstem reflexes, and overall survival. In most trials, randomization was 2 hours or more after ROSC. Based on graphical plots in each paper, groups differed by 1 °C at 3 to 4 hours after randomization and by 2 °C at 4 to 5 hours after randomization, though with considerable overlap.

HACA, hypothermia after cardiac arrest; TTM, targeted temperature management; HYPERION, Therapeutic Hypothermia after Cardiac Arrest in Nonshockable Rhythm; IHCA, in-hospital cardiac arrest; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; T, temperature.

†Data for TTM with mild hypothermia group if pooled data not in paper. † †Time from ROSC.
Second, are the enrolled patients representative of all cardiac arrest patients (Table 1)? TTM and TTM2 included patients with presumed cardiac cause of cardiac arrest and excluded patients resuscitated from unwitnessed asystole. These criteria resulted in a very “cardiac” cohort with shockable rhythms in 79% [26] and 74% [27], respectively, and with ST elevation myocardial infarction in 41% [26] and 41% [27], respectively. This is a very important group of OHCA patients, and perhaps represents the group from which the largest proportion of survivors arise. However, randomized cohorts exclude many patients encountered at most clinical centers, for whom clinicians also must decide on TTM treatment.

**TTM-HYPOTHERMIA IN NEONATES AND CHILDREN**

Use of TTM-hypothermia in adult cardiac arrest is also informed by clinical studies in children and neonates. Extrapolation from children to adults should recognize that therapeutic effects may differ in the developing brain relative to the adult brain. Also, the underlying insult leading to cardiac arrest may be quite different between these populations. Regardless, cardiac arrest in children and hypoxic-ischemic brain injury in neonates provide opportunity to test the efficacy of TTM-hypothermia for improving brain recovery after global hypoxia-ischemia.

The clinical evidence for use of TTM-hypothermia after hypoxic-ischemic brain injury (HIBI) in neonates is very robust. A recent systematic review identified 28 randomized trials enrolling neonates who underwent TTM-hypothermia (n = 1,832) or normothermia (n = 1,760) [64]. Survival was higher for TTM-hypothermia infants (74% vs. 63%) with similar results across several subgroups and methods of cooling.

There are several key differences between the clinical use of TTM-hypothermia in neonates and adults. First, the initiation of treatment for HIBI is sooner than usual for adult cardiac arrest. Most trials enroll neonates with HIBI within 6 hours of birth and as soon as possible [64]. Because neonates have a large body surface area relative to body volume, rapid control of temperature is much easier than in adult cardiac arrest. Thus, delays in achieving separation of treatment groups were not an issue in clinical trials. Secondly, clinicians treat HIBI with TTM-hypothermia for 72 hours. This longer duration of treatment spans more of the time period when seizures, cerebral edema, and other clinical sequelae of brain ischemia are expected. Finally, determining outcomes after HIBI in neonates is less often confounded by WLST as it is in adults.

Differeat treatment of children after cardiac arrest was less...
RAPID INDUCTION OF HYPOTHERMIA IN ADULTS

Several adult trials demonstrate the feasibility of very rapid initiation of TTM-hypothermia, but these trials treated patients differently only for a short period of time. In a trial of an intranasal cooling intervention, temperatures were lower in the intervention group between 25 and 182 minutes after ROSC, but there was no

Table 2. Features of patients with different illness severities

<table>
<thead>
<tr>
<th>Feature</th>
<th>Low risk</th>
<th>Moderate risk</th>
<th>Severe risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCAC [42]</td>
<td>PCAC2</td>
<td>PCAC3</td>
<td>PCAC4</td>
</tr>
<tr>
<td>Shockable rhythm (%)</td>
<td>50</td>
<td>34</td>
<td>18</td>
</tr>
<tr>
<td>CPR duration (min)</td>
<td>11 (5–11)</td>
<td>12 (6–12)</td>
<td>22 (12–22)</td>
</tr>
<tr>
<td>Pupillary reflex present (%)</td>
<td>94</td>
<td>79</td>
<td>36</td>
</tr>
<tr>
<td>Survival (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTM-hypothermia</td>
<td>64&lt;sup&gt;a&lt;/sup&gt;</td>
<td>55&lt;sup&gt;a&lt;/sup&gt;</td>
<td>15&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Control</td>
<td>78&lt;sup&gt;a&lt;/sup&gt;</td>
<td>33&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.4&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Good outcome (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTM-hypothermia</td>
<td>61&lt;sup&gt;a&lt;/sup&gt;</td>
<td>48</td>
<td>13&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Control</td>
<td>75&lt;sup&gt;a&lt;/sup&gt;</td>
<td>33</td>
<td>4.7&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>rCAST [75]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 5.5</td>
<td>6–14</td>
<td>&gt; 14</td>
<td></td>
</tr>
<tr>
<td>Shockable rhythm (%)</td>
<td>93</td>
<td>64</td>
<td>28</td>
</tr>
<tr>
<td>CPR duration (min)</td>
<td>13 (10–17)</td>
<td>20 (14–27)</td>
<td>32 (25–39)</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>6.1 ± 2.8</td>
<td>8.2 ± 5.0</td>
<td>12.2 ± 4.6</td>
</tr>
<tr>
<td>Survival (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTM-hypothermia</td>
<td>94</td>
<td>83&lt;sup&gt;a&lt;/sup&gt;</td>
<td>42</td>
</tr>
<tr>
<td>Control</td>
<td>98</td>
<td>70&lt;sup&gt;a&lt;/sup&gt;</td>
<td>34</td>
</tr>
<tr>
<td>Good outcome (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTM-hypothermia</td>
<td>82</td>
<td>52&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6.5</td>
</tr>
<tr>
<td>Control</td>
<td>91</td>
<td>38&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.5</td>
</tr>
<tr>
<td>Lactate (mmol/L) [76]</td>
<td>&lt; 7</td>
<td>≥ 7 and &lt; 12</td>
<td>≥ 12</td>
</tr>
<tr>
<td>Shockable rhythm (%)</td>
<td>63</td>
<td>55</td>
<td>41</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>5.2 (3.7–6.1)</td>
<td>9.1 (7.9–10.2)</td>
<td>14.9 (13.2–18.0)</td>
</tr>
<tr>
<td>Survival (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTM-hypothermia</td>
<td>82</td>
<td>78</td>
<td>58</td>
</tr>
<tr>
<td>Control</td>
<td>90</td>
<td>82</td>
<td>52</td>
</tr>
<tr>
<td>Good outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTM-hypothermia</td>
<td>60</td>
<td>44</td>
<td>22&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Control</td>
<td>61</td>
<td>37</td>
<td>13&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Electroencephalography [31]</td>
<td>Continuous normal background by 12 hr</td>
<td>Burst-suppression, GPDs without suppressed background, continuous or discontinuous low voltage (&lt; 20 µV) activity</td>
<td>Suppression (&lt; 10 µV) of background at 12 or 24 hr</td>
</tr>
<tr>
<td>Survival (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTM-hypothermia</td>
<td>89</td>
<td>70&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
</tr>
<tr>
<td>Control</td>
<td>87</td>
<td>51&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
</tr>
<tr>
<td>Good outcome (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTM-hypothermia</td>
<td>88</td>
<td>66&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
</tr>
<tr>
<td>Control</td>
<td>81</td>
<td>45&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
</tr>
<tr>
<td>mCAHP [77]</td>
<td>&lt; 80</td>
<td>80–105</td>
<td>&gt; 105</td>
</tr>
<tr>
<td>Favorable outcome overall</td>
<td>70</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td>Odds ratio (TTM-hypothermia vs. control)</td>
<td>1.45 (1.18–1.77)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.23 (0.99–1.52)</td>
<td>2.21 (1.47–3.34)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Values are presented as number only, median (interquartile range), or mean ± standard deviation. Studies comparing outcomes between TTM-hypothermia and higher temperature strategies (control) report different treatment effects in patients with different illness severities. These strata of patients differ in clinical features. Hypothermia benefits moderate risk or severe risk groups but does not benefit low-risk groups. TTM at 36 °C was superior in some low-risk groups (PCAC2) who more closely resemble clinical trial cohorts. The mCAHP score is an exception, where TTM-hypothermia was beneficial for low risk and severe risk, but not moderate risk groups.

PCAC, Pittsburgh Cardiac Arrest Category; CPR, cardiopulmonary resuscitation; TTM-hypothermia, targeted temperature management with mild hypothermia; rCAST, revised post-cardiac arrest syndrome for therapeutic hypothermia score; mCAHP, modified cardiac arrest hospital prognosis.

<sup>a</sup>Difference between TTM-hypothermia and control were statistically significant.
change in 90-day survival (17.8% vs. 15.6%) or good functional recovery (16.6% vs. 13.5%) [18].

Rapid infusions of cold intravenous fluids in the ambulance after ROSC can quickly reduce temperature [72,73]. A trial of post-ROSC cold intravenous fluids allowed patients to reach target temperature about 1 hour faster than usual care patients but did not treat patients differently after hospital arrival [16]. Rapid infusion of cold intravenous fluids during OHCA also reduced core temperature by the time of hospital arrival [17]. All the trials using cold intravenous fluid either after ROSC [16,73,74] or during arrest [17] are complicated by an apparent adverse effect of fluids on cardiopulmonary function, including higher risk of death at the scene, rearrest, or pulmonary edema at the hospital.

Thus, rapid initiation of TTM-hypothermia is possible, but trials to date result in temperature differences between groups for only 1 to 2 hours, and all patients were treated similarly during the key therapeutic windows (Fig. 1). Consequently, these trials did not detect changes in neurological recovery [16,17,73,74].

ILLNESS SEVERITY INFLUENCES TREATMENT EFFECT OF TTM–HYPOTHERMIA

One interpretation of conflicting clinical trial results is that TTM-hypothermia offers less benefit for certain cohorts of adult patients, such as the cardiac population in TTM and TTM2 trials with high probability of good outcome [26,27], but may be more beneficial for other cohorts of patients with lower probability of good outcome, such as the more frequent respiratory arrest population in the HYPERION trial [62]. Observational studies support a differential treatment effect for TTM-hypothermia across subgroups, and these studies have an advantage over the clinical trials in that they include a more diverse cohort of patients (Table 2) [31,42,75–77].

Using initial clinical severity to stratify patients, one series from a single North American center took advantage of practice variation after the 2013 TTM Trial to compare 1,319 OHCA and IHCA patients treated with TTM-hypothermia (33 °C, n = 728) versus TTM at 36 °C (n = 591) [42]. For 184 patients with severe cerebral edema on admission and 234 patients with a highly malignant EEG, outcomes were poor regardless of TTM treatment. Among 911 patients with neither severe cerebral edema nor highly malignant EEG, there was an interaction between TTM-hypothermia choice and clinical severity measured using the Pittsburgh Cardiac Arrest Category (PCAC) score. PCAC uses clinical exam to define patients as moderate coma with preserved brainstem reflexes (PCAC2), moderate coma with severe cardiopulmonary dysfunction (PCAC3) and deep coma with missing brainstem reflexes (PCAC4).

TTM-hypothermia was associated with higher survival for PCAC3 (55% vs. 33%) and PCAC4 (15% vs. 5%) patients, higher good functional recovery for PCAC3 patients (24% vs. 6%) and higher recovery without severe disability for PCAC4 patients (13% vs. 5%). Conversely, TTM at 36 °C was associated with higher survival (78% vs. 64%) and survival without severe disability (75% vs. 61%) for PCAC2 patients.

A separate clinical severity score was used to stratify 1,111 OHCA patients undergoing TTM in the nationwide Japanese Association for Acute Medicine OHCA database [75]. The revised post-cardiac arrest syndrome for therapeutic hypothermia (rCAST) score uses historical and clinical information at hospital admission to describe patients as low severity (≤ 5.5), moderate severity (≥ 6 and ≤ 14.5), or high severity (≥ 14.5). Patients were treated with TTM-hypothermia (33–34 °C) or higher temperature (35–36 °C). Among moderate–severity patients, TTM-hypothermia was associated with higher 30-day survival (83% vs. 70%) and good functional recovery (52% vs. 38%). However, there was no association of temperature choice with survival or functional recovery for low–severity or high–severity patients.

Initial blood lactate levels in the same Japanese database stratified 435 patients into mild (< 7 mmol/l, n = 139), moderate (≥ 7 and < 12 mmol/l, n = 182) or severe (≥ 12 mmol/l, n = 114) groups [76]. Among severe patients but not among mild or moderate patients, TTM–hypothermia (32–34 °C) compared to TTM at higher temperatures (35–36 °C) was associated with higher 30-day survival (58% vs. 52%) and favorable functional recovery (22% vs. 13%), even when comparisons were adjusted for other patient characteristics.

EEG defined mild, moderate, and severe encephalopathy in a series of 479 OHCA and IHCA patients from five hospitals [31]. Mild encephalopathy comprised a continuous EEG background, and severe encephalopathy comprised a prolonged suppression of background. Other patterns and suppressed background becoming continuous by 24 hours were considered moderate. TTM-hypothermia was associated with good outcome in moderate–encephalopathy patients (66% vs. 45%), but not in those with mild (88% vs. 81%) or severe (0% vs. 0%) encephalopathy. This study had several limitations, including the fact that EEG was sometimes obtained after initiation of TTM regimen and was more often missing among the 36 °C group.

Another analysis used historical factors about the resuscitation in the modified Cardiac Arrest Hospital Prognosis score to define mild (< 80), moderate (≥ 80 and < 105), or severe (≥ 105) risk groups among 2,723 OHCA patients in the Sudden Death Expertise Center registry and 4,202 OHCA patients in the Resuscitation Outcomes Consortium database [77]. In both databases and in
pooled data, TTM at 33 to 36 °C was associated with both survival and favorable functional recovery in low and severe risk groups, but this association was weaker in moderate-severity groups.

Thus, observational data from multiple cohorts suggest that the treatment effect of TTM-hypothermia depends on illness severity. The groups of patients who appear to benefit from TTM-hypothermia differ in many respects from the cohorts of patients enrolled in clinical trials that did not detect benefit (Table 1) [24, 26–28,62]. Clinicians should consider that imaging, EEG, or clinical exam can identify some patients whose brain injury is so severe that they will do poorly regardless of any current therapy [31,42,75]. Clinical or laboratory features also can identify mildly injured patients whose favorable prognosis is not affected by choice of TTM regimen [31,76,77] or who may even do better with TTM at 36 °C instead of TTM-hypothermia [42]. Future studies need to consider that individual patient characteristics may determine the treatment effect of TTM-hypothermia, and research should explore how to select the best regimen and duration of treatment for each individual patient.

**REAL-WORLD IMPLEMENTATION AND DE-IMPLEMENTATION OF TTM–HYPOTHERMIA**

Overall survival improved for cardiac arrest patients in many places after implementation of TTM in the early 2000s [78,79]. However, it is impossible to determine if this trend for improvement resulted from the effects of temperature or simply from the adoption of more comprehensive and optimistic protocols of care in this population. Changes in practice after the TTM Trial [25] provides another opportunity to assess the effects of TTM-hypothermia, because many places de-implemented TTM-hypothermia protocols in favor of normothermia but presumably maintained other aspects of protocolized post-cardiac arrest care.

Single centers have reported worsened outcomes with de-implementation of TTM–hypothermia. In 782 OHCA patients transported to one North American center from 2010 to 2017, 453 received targeted temperature management with either TTM-hypothermia (33 °C, n = 258) prior to 2014 or TTM at 36 °C (n = 195) from 2014 to 2017 [80]. TTM-hypothermia was associated with a nonsignificant higher survival (45% vs. 36%) and significantly higher favorable functional recovery (40% vs. 30%). One Australian institution routinely treated patients who had ventricular fibrillation OHCA with TTM-hypothermia (33 °C) prior to 2013 (n = 24) but adopted a practice of TTM at 36 °C after 2014 (n = 52) [81]. TTM-hypothermia was associated with higher survival (71% vs. 58%) and favorable functional status at hospital discharge (71% vs. 56%). These investigators noted that patients treated at 36° had higher rates of fever and less reliable maintenance of target temperature.

Larger datasets show similar trends. In the Australia New Zealand Intensive Care Society Adult Patients Database, investigators were able to compare patients admitted to the ICU after OHCA from prior to December 2013 (n = 4,450) and after December 2013 (n = 5,184) [79]. Temperature data suggest lower temperatures were targeted prior to 2013 and rates of fever increased after 2013. While the overall survival did not differ between the two time periods (47.6% vs. 46.6%), there was a trend for improving survival over time prior to 2013 (1.3%/yr) that reversed after 2013 (~0.6%/yr).

These de-implementation studies are complex to interpret because many other aspects of cardiac arrest care change over time, and implementation of TTM-hypothermia may be correlated with secular trends in resuscitation and also with many other post-cardiac arrest practices such as sedation or timing of prognostic testing. For example, in 3,925 patients from the registry of the Paris Sudden Death Expertise Center, rates of TTM use at any temperature (33–36 °C) declined from 55% in 2011 to 37% in 2017 [82]. During this interval, rates of survival to ICU discharge increased (from 20% to 26%) and favorable functional recovery did not change (from 19% to 23%). However, during this time period, rates of bystander CPR and the proportion of patients with no-flow time ≤ 3 minutes increased while the proportion of patients with post-reperfusion shock decreased. During the whole time period, receipt of TTM was associated with higher survival from the ICU (37% vs. 20%) and favorable functional recovery (33% vs. 15%), even when adjusting for the other secular trends.

Thus, reports suggest possible risks to abandoning TTM-hypothermia [79–82]. However, the available data do not reveal whether these effects are mediated by choice of goal temperature, by an associated change in practice style, or by changes in the patient characteristics over time.

**CONCLUSION**

Implementation of TTM-hypothermia after 2002 transformed the clinical care of adults with coma after resuscitation from cardiac arrest, and survival for patients admitted to the intensive care after cardiac arrest increased over the next two decades. Subsequent methodologically more rigorous trials in adults have not detected any benefit, prompting speculation that the regimen of care determines outcome more than the particular target temperature for the enrolled cohorts.
Post hoc analyses and observational data suggest some explanations for these findings. Adult trials may enroll many patients who are not likely to respond to TTM-hypothermia. Treatment effects may differ between strata of patients with different illness severity. TTM-hypothermia may have smaller or no effect on patients with milder severities and no effect on patients who are completely devastated. Despite the feasibility of rapid temperature manipulation, larger multicenter trials based in the ICU do not clearly achieve separation of treatment between groups within the therapeutic window of 4 hours of reperfusion suggested by preclinical data. Finally, the 24-hour TTM intervention most studied in adults is less than the optimal duration in animals or the effective durations in neonates or children. Ideally, any treatment would be titrated to the needs and response of the individual patient.

At this time, TTM-hypothermia is one tool for the care of select patients after cardiac arrest. If initiated rapidly, it can reduce seizures, brain edema and reduce metabolic demand when oxygen delivery is impaired. Using TTM-hypothermia in patients with risks of these temperature-sensitive problems would be reasonable practice based on preclinical and observational data. Aggressive critical care with or without TTM-hypothermia may be sufficient for many patients who resemble the cohorts enrolled in recent large trials, particularly those with clinical features suggesting >50% probability of survival. Future trials should enroll patients with well-defined injury, measure putative mediators of TTM effects or temperature-sensitive conditions, and focus on titration of temperature depth and duration-based patient condition.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Post-acute sequelae of SARS-CoV-2 syndrome presenting as postural orthostatic tachycardia syndrome

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The novel SARS-CoV-2 emerged in 2019, and the global COVID-19 pandemic continues into 2022. It has been known that a subset of patients develops chronic, debilitating symptoms after otherwise complete recovery from acute infection of COVID-19. Multiple terms have been used to describe this constellation of symptoms, including long COVID, long-haul COVID, and post-acute sequelae of SARS-CoV-2 syndrome (PASC). PASC is broadly defined as a wide range of new, returning, or ongoing symptoms at least four weeks after infection. Those patients are often seen in emergency departments after acute COVID-19 infection, but their symptoms are not adequately managed because the underlying pathophysiology of PASC is not well understood. Among patients with PASC, postural orthostatic tachycardic syndrome (POTS) has been increasingly recognized. POTS is one of the most common forms of autonomic dysfunction and defined by a sustained orthostatic tachycardia during active standing or head-up tilt test in the absence of orthostatic hypotension or other cardiopulmonary diseases. Because POTS is a treatable condition, it is important to recognize POTS among PASC patients. Herein, we reviewed the current literature on POTS and dysautonomia in PASC in order to better understand the overlap and distinction between these pathologies.

Keywords: Post-acute COVID-19 syndrome; Postural orthostatic tachycardia syndrome; Autonomic nervous system; Postural tachycardia syndrome; Post-acute COVID-19 syndrome
INTRODUCTION

The novel SARS-CoV-2 emerged in 2019, and the global COVID-19 pandemic continues into 2022. Since the introduction of vaccination against COVID-19, the overall mortality has been declining [1–3]. However, a subset of patients develop chronic debilitating symptoms after complete recovery from acute COVID-19 infection. Several terms have been used to describe this constellation of symptoms, including long COVID, long-haul COVID, and post-acute sequelae of SARS-CoV-2 (PASC) syndrome. PASC is broadly defined as a wide range of new, returning, or ongoing symptoms at least 4 weeks after infection [4]. Typical symptoms include chronic fatigue, chronic nausea, indigestion, constipation, brain fog, orthostatic tachycardia, and exertional dyspnea among many others. Symptoms are often severe, and most patients are on disability or modified independence. Due to the severity of the symptoms, these patients are often seen in emergency departments (EDs) after acute COVID-19 infection. However, the pathophysiology and treatments for PASC are not well established.

Although PASC has multiple manifestations, postural orthostatic tachycardia syndrome (POTS) has been increasingly recognized among patients with PASC. The diagnostic definition of POTS includes symptoms that have lasted longer than three months and a sustained heart rate increase of at least 30 beats/min or a heart rate of 120 beats/min or more within 10 minutes of standing or during head-up tilt test (HUTT) in the absence of orthostatic hypotension (OH) while reproducing typical symptoms [5]. The symptoms of POTS often include dizziness, palpitations, fatigue, headache, nausea, pre-syncope, tunneling of vision, and brain fog.

Many POTS symptoms are thought to be due to autonomic vasomotor failure. Because viral infection can host various chronic neurological conditions, such as Guillain-Barre syndrome, POTS can possibly occur as a post-COVID-19 autonomic nerve involvement. However, the prevalence of POTS among PASC varies greatly in the literature, and the association between PASC and POTS is unclear. Herein, the current literature on POTS and dysautonomia in PASC is reviewed. The results can be used to better understand the overlap and distinction between these pathologies, leading to better understanding of their etiology, treatment, and directions for future research.

METHODS

A review of literature on the association of POTS with COVID-19 infection or postinfection was conducted using the Medline (Pub-Med) database. The search terms used were “COVID-19 and POTS,” “SARS-CoV-2 and POTS,” “COVID-19 and postural orthostatic tachycardic syndrome,” and “SARS-CoV-2 and postural orthostatic tachycardia syndrome,” dated from March 2020 to September 2022. The searches yielded a total of 29 references for potential inclusion based on criteria of English language articles addressing POTS (as in postural orthostatic tachycardia syndrome and not other language uses of POTS) in clinical or seropositive COVID-19 infection or post-COVID-19 infection and case report, clinical study, clinical trial, multicenter study, observational study, or randomized controlled study. Review articles were excluded. Finally, 22 papers were analyzed.

RESULTS

Case reports and case series of POTS after acute COVID-19 infection in the early COVID-19 pandemic

The first reported case of POTS early in the pandemic (March 2020) occurred in Orange County, CA, USA and was published by Miglis et al. [6]. A 26-year-old nurse presented with mild cough and an itchy throat, immediately followed by palpitations, fatigue, and mild shortness of breath. For the next month, the orthostatic intolerance (OI) symptoms worsened. The heart rate response to HUTT showed a sustained increase greater than 30 beats/min that persisted for the duration of the tilt during autonomic testing. Based on these findings, she was diagnosed with POTS. Since then, similar cases have been reported, mainly from the USA but a few from European and Asian countries; most patients were young females who presented with fatigue, headache, dizziness, chest pain, and palpitations after COVID-19 infection [6–20]. POTS was diagnosed based on heart rate and blood pressure responses to the HUTT and active standing test in addition to symptoms of chronic fatigue, brain fog, palpitation, OI, and various gastrointestinal (GI) symptoms. POTS symptoms occurred typically a few weeks after the initial upper respiratory infection (URI) symptoms of COVID-19; however, in some cases, POTS symptoms first presented as URI. Most cases included typical symptoms of POTS such as fatigue, headache, dizziness, chest pain, palpitations, nausea/vomiting, exercise intolerance, and insomnia. Case reports and case series of post-COVID-19 POTS are summarized in Table 1 [6–20].

Observational studies of post-COVID-19 patients focusing on autonomic functions

In 2021, Buioite Stella et al. [21] published a prospective multidomain observational study of autonomic symptoms and signs in post-COVID-19 patients. They recruited patients who presented...
Mixed hyperadrenergic symptoms and autonomic test results consistent with hyperadrenergic POTS with normal serum norepinephrine level.

POTS symptoms 3–4 wk after SARS-CoV-2 infection. POTS diagnosis confirmed using the HUTT.

Among patients, 80% required pharmacotherapy and 85% had residual symptoms 6–8 mo after COVID-19. Three patients returned to work full time, and five were able to work full time from home with some accommodations.

Complicated hospital course followed by diagnosis of POTS and multiple other afflictions. Four mo after onset of COVID-19, the patient had no orthostatic tachycardia or hypotension.

New-onset POTS following COVID-19, symptomatically responsive to low-dose bisoprolol.

Patient with hyperadrenergic POTS with history of ablation experienced reduction in POTS symptoms after periods of type II AV block and both Mobitz I and Mobitz II second-degree AV block following SARS-CoV-2 infection.

Met criteria for POTS. After treatment with ivabradine, symptoms significantly improved. The patient was advised to engage in daily exercise.

Among patients in the series, four of six showed findings potentially compatible with POTS, including two patients with both hypertension and tachycardia based on the HUTT, consistent with a hyperadrenergic POTS subtype.

Diagnosed with POTS, mast cell activation syndrome, and aPL-positivity and showed significant improvement. He also started hydroxychloroquine for persistent aPL.

All three participants met criteria for myalgic encephalitis and chronic fatigue syndrome at 6 mo after the onset of symptoms. All patients had profound POTS on testing.

All three patients were diagnosed with POTS and received treatment but remained symptomatic and on sick leave.

After SARS-CoV-2 infection, the 11-year-old male presented with multisystemic inflammation syndrome in children and the 16-year-old female presented with POTS.

The patient developed POTS symptoms after a few days of COVID-19 infection. A cutaneous nerve biopsy and QSART showed small fiber and sudomotor neuropathy.

Case series of 11 patients with PASC referred to Typical symptoms included chronic fatigue and palpitation. All patients had normal echocardiogram.

Table 1. Case reports and series of POTS after acute COVID-19 infection

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient characteristic</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miglis et al. [6]</td>
<td>26-year-old female</td>
<td>Mixed hyperadrenergic symptoms and autonomic test results consistent with hyperadrenergic POTS with normal serum norepinephrine level.</td>
</tr>
<tr>
<td>Kanjiwal et al. [7]</td>
<td>36-year-old female</td>
<td>POTS symptoms 3–4 wk after SARS-CoV-2 infection. POTS diagnosis confirmed using the HUTT.</td>
</tr>
<tr>
<td>Blitshteyn and Whitelaw [14]</td>
<td>20 patients with persistent symptoms after acute COVID-19 infection between April and December 2020</td>
<td>Among patients, 80% required pharmacotherapy and 85% had residual symptoms 6–8 mo after COVID-19. Three patients returned to work full time, and five were able to work full time from home with some accommodations.</td>
</tr>
<tr>
<td>Umapathi et al. [8]</td>
<td>39-year-old male</td>
<td>Complicated hospital course followed by diagnosis of POTS and multiple other afflictions. Four mo after onset of COVID-19, the patient had no orthostatic tachycardia or hypotension.</td>
</tr>
<tr>
<td>Ocher et al. [10]</td>
<td>32-year-old female</td>
<td>Patient with hyperadrenergic POTS with history of ablation experienced reduction in POTS symptoms after periods of type II AV block and both Mobitz I and Mobitz II second-degree AV block following SARS-CoV-2 infection.</td>
</tr>
<tr>
<td>O’Sullivan et al. [11]</td>
<td>22-year-old female</td>
<td>Met criteria for POTS. After treatment with ivabradine, symptoms significantly improved. The patient was advised to engage in daily exercise.</td>
</tr>
<tr>
<td>Goodman et al. [16]</td>
<td>Nonhospitalized COVID-19 patients with persistent, disabling symptoms due to dysautonomia presenting to the dysautonomia clinic</td>
<td>Among patients in the series, four of six showed findings potentially compatible with POTS, including two patients with both hypertension and tachycardia based on the HUTT, consistent with a hyperadrenergic POTS subtype.</td>
</tr>
<tr>
<td>Schofield [17]</td>
<td>50-year-old male</td>
<td>Diagnosed with POTS, mast cell activation syndrome, and aPL-positivity and showed significant improvement. He also started hydroxychloroquine for persistent aPL.</td>
</tr>
<tr>
<td>Petracek et al. [13]</td>
<td>Patients had confirmed or probable exposure to COVID-19 during the pandemic period and had been referred to a chronic fatigue clinic</td>
<td>All three participants met criteria for myalgic encephalitis and chronic fatigue syndrome at 6 mo after the onset of symptoms. All patients had profound POTS on testing.</td>
</tr>
<tr>
<td>Johansson et al. [12]</td>
<td>37-year-old male, 42-year-old female, and 28-year-old female</td>
<td>All three patients were diagnosed with POTS and received treatment but remained symptomatic and on sick leave.</td>
</tr>
<tr>
<td>Buchhorn et al. [15]</td>
<td>11-year-old male and 16-year-old female</td>
<td>After SARS-CoV-2 infection, the 11-year-old male presented with multisystemic inflammation syndrome in children and the 16-year-old female presented with POTS.</td>
</tr>
<tr>
<td>Bosco and Titano [18]</td>
<td>27-year-old female</td>
<td>The patient developed postexercise fatigue, orthostatic intolerance, headaches, and generalized aches at 5 wk after acute COVID–19 infection.</td>
</tr>
<tr>
<td>Agnihotri et al. [19]</td>
<td>47-year-old female</td>
<td>The patient developed POTS symptoms after a few days of COVID–19 infection. A cutaneous nerve biopsy and QSART showed small fiber and sudomotor neuropathy.</td>
</tr>
<tr>
<td>Desai et al. [20]</td>
<td>Case series of 11 patients with PASC referred to Typical symptoms included chronic fatigue and palpitation. All patients had normal echocardiogram.</td>
<td></td>
</tr>
</tbody>
</table>

POTS, postural orthostatic tachycardia syndrome; HUTT, head-up tilt table test; AV, atrioventricular; aPL, antiphospholipid syndrome; QSART, quantitative sudomotor axon reflex test; PASC, post-acute sequelae of SARS-CoV-2.

with persistent symptoms and/or delayed complications between 4 weeks and 9 months from the onset of COVID-19 infection and were referred to the post–COVID-19 ambulatory service of the University Hospital and Health Services of Trieste, Italy, between February 15 and May 15 2021. Among 180 patients, 13.8% showed OH during the 3-minute active standing test. However, in the short standing test protocol, none of the patients met the criteria for POTS. Subsequently, Wallukat et al. [22] performed a case control study in which functionally active autoantibodies (fAABs) targeting G-protein coupled receptors (GPCR-fAABs) were detected in patients suffering from various long–COVID-19 symptoms. Blood sera were obtained from 31 patients; 29 who were still suffering from post–COVID-19 symptoms after recovery from acute disease and two who were symptom-free. All participants tested positive based on polymerase chain reaction (PCR). Among the patients, seven had POTS. The control group had normal laboratory values. All 31 investigated patients had between two and seven types of GPCR-fAABs. Around the same time, Shouman et al. [23] published a retrospective chart review on post–COVID-19 patients. They included all patients with confirmed history of COVID-19 infection who were referred for autonomic testing at the Mayo Clinic in Rochester, MN or Jacksonville, FL, USA between March 2020 and January 2021 and identified 27 patients who met the inclusion criteria. The results included symptoms after acute infection such as lightheadedness (93%), orthostatic headache (22%), syncope (11%), hyperhidrosis (11%), and burning pain (11%). Orthostatic symptoms without tachycardia were the most common clinical observation. In this population, 22% of patients fulfilled the criteria for POTS, with most patients experiencing orthostatic symptoms showing a normal tilt test. Most recently, Jamal et al.
[24] performed a prospective, longitudinal, observational evaluation of patients with PASC symptoms, defined as at least one clinical sequela lasting longer than 4 weeks after acute COVID-19 infection. Patients with abnormal cardiopulmonary functions and prior history of autonomic symptoms were excluded. A total of 24 patients underwent 21-minute HUTT after resting for at least 5 minutes. If the initial HUTT response was normal, the authors administered 0.4-mg sublingual nitroglycerin and observed the response for an additional 15 minutes. Provoked OI (POI) was defined by a heart rate increase of 30 beats/min with no significant changes in blood pressure after administration of sublingual nitroglycerin. In the study, four patients showed POTS and 15 patients showed POI during the HUTT. Only one of 24 patients had normal response on the HUTT, indicating underlying autonomic dysfunction in the majority of post-COVID-19 patients. Observational studies on post-COVID-19 POTS are summarized in Table 2 [21–24].

Case reports of POTS after COVID-19 vaccination

We found three case reports of POTS after COVID-19 vaccination. Hermel et al. [25] reported a previously healthy 40-year-old male patient who developed POTS symptoms after a single dose of BNT162b2 SARS-CoV-2 vaccine from Pfizer. Her predominant symptoms included fatigue, brain fog, headache, sinus tachycardia, and dizziness. The patient underwent full autonomic testing, which showed normal heart rate variability and Valsalva reactions. However, the HUTT showed significant and sustained elevation of heart rate > 40 beats/min, a typical symptom of POTS. Reddy et al. [26] reported a previously healthy 42-year-old male patient who developed POTS symptoms approximately 6 days after receiving the BNT162b2 SARS-CoV-2 vaccine. Extensive medical workup revealed normal heart functions and hormone levels except for sinus tachycardia. In the third case, Park et al. [27] reported a previously healthy 40-year-old male patient who presented with an 8-week history of intermittent headache, palpitation fatigue, and dyspnea, which developed 1 week after receiving the first dose of the Moderna COVID-19 vaccine. The patient underwent full autonomic testing, which showed normal heart rate variability and Valsalva reactions. However, quantitative sudomotor axon reflex test (OSART) showed reduced reflex sweating in the lower extremity. The HUTT showed orthostatic tachycardia with heart rate increasing from 72 to 110 beats/min without significant change in blood pressure. In this case, the patient’s symptoms were nearly resolved at the 5-month follow-up. The case reports of POTS after COVID-19 vaccination are summarized in Table 3 [25–27].

Table 2. Observational studies of autonomic functions in post-COVID-19 patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Exposure and outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wallukat et al. [22]</td>
<td>Blood serum of 31 patients after recovery from acute SARS-CoV-2 infection</td>
<td>Investigated whether fAABs targeting GPCR-fAABs can be detected in patients suffering from various long COVID-19 symptoms; seven patients had POTS. All 31 investigated patients had between two and seven types of GPCR-fAABs.</td>
</tr>
<tr>
<td>Buoite Stella et al. [21]</td>
<td>Patients referred to the post-COVID-19 ambulatory service of the University Hospital and Health Services of Trieste between February 15 and May 15, 2021</td>
<td>Administered the COMPASS-31 questionnaire to a sample of post-COVID-19 patients with and without neurological complaints. Active stand test indicated OH in 13.8% of the sample; POTS was not found in any of the subjects. OH was mainly characterized by decreased diastolic blood pressure after 3 min of standing (−15±3 mmHg).</td>
</tr>
<tr>
<td>Shouman et al. [23]</td>
<td>Patients with confirmed history of SARS-CoV-2 infection referred for autonomic testing for symptoms concerning parainfectious/postinfectious autonomic dysfunction</td>
<td>Among 27 patients, 17 (63%) had abnormalities on autonomic function testing. The most common autonomic presentation was OI, and 22% of patients fulfilled the criteria for POTS.</td>
</tr>
<tr>
<td>Jamal et al. [24]</td>
<td>Prospective, observational study of patients with PASC syndrome who presented with autonomic symptoms</td>
<td>A total 24 patients underwent full autonomic testing; 23 had OI on the HUTT, with four demonstrating POTS, 15 POI after administration of nitroglycerin, three neurocardiogenic syncope, and one OH.</td>
</tr>
</tbody>
</table>

fAAB, functionally active autoantibody; GPCR, G-protein coupled receptors; POTS, postural orthostatic tachycardia syndrome; COMPASS-31, Composite Autonomic Symptom Score 31; OH, orthostatic hypotension; OI, orthostatic intolerance; PASC, post-acute sequelae of SARS-CoV-2; HUTT, head-up tilt table test; POI, provoked orthostatic intolerance.

Table 3. Case reports of POTS after COVID-19 vaccination

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient characteristic</th>
<th>Exposure and outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hermel et al. [25]</td>
<td>46-year-old female</td>
<td>POTS symptoms after a single dose of BNT162b2 SARS-CoV-2 vaccine from Pfizer.</td>
</tr>
<tr>
<td>Reddy et al. [26]</td>
<td>42-year-old male</td>
<td>POTS symptoms approximately 6 days after BNT162b2 SARS-CoV-2 vaccine from Pfizer. Workup indicated POTS.</td>
</tr>
<tr>
<td>Park et al. [27]</td>
<td>40-year-old male</td>
<td>An 8-wk history of intermittent headache, palpitation fatigue, and dyspnea that developed 1 wk after receiving the first dose of Moderna COVID-19 vaccine. Workup revealed POTS and sudomotor dysfunction.</td>
</tr>
</tbody>
</table>

POTS, postural orthostatic tachycardia syndrome.
DISCUSSION

Several infectious pathogens can trigger chronic sequelae after resolution of acute infections, referred to as post-acute infection syndromes (PAISs). A few PAISs are well-characterized, such as Guillain–Barre syndrome or postpolio syndrome [28]. However, the pathophysiology of PAISs is largely unknown. Therefore, PASC syndrome is very broadly defined as a wide range of any new, returning, or ongoing symptoms at least 4 weeks after acute COVID-19 infection [4]. Despite the uncertainty of the condition, several large cohort studies across the globe have involved longitudinal observation of chronic symptoms beyond several months after acute infection since the pandemic of COVID-19. From these collective efforts, autonomic dysfunction presenting as POTS in PASC has emerged early in the COVID-19 pandemic.

POTS is among the most frequent causes of dysautonomia in the USA and is associated with increased disability and poor quality of life [29]. POTS patients are also frequent visitors to the ED; on average, patients with POTS have nine ED visits prior to diagnosis [30]. POTS disproportionately affects young women, preventing many of them from participating in school or work due to the symptom burden [29]. Although the true prevalence is unknown, POTS is estimated to affect approximately 0.1% to 1% of the US population [31]. In addition, POTS is a clinical syndrome with heterogeneous etiologies. As a final common pathway from multiple different pathophysiological processes, POTS symptoms are primarily caused by impaired vasomotor control of blood volume. For example, damage to sympathetic vasomotor nerves prevents the compensatory increase in systemic vascular resistance to orthostatic changes and/or exercise, causing typical POTS symptoms such as lightheadedness, brain fog, and chronic fatigue. Simultaneously, central, compensatory activation of the sympathetic nervous system causes tachycardia as a response to a reduced cardiac preload; however, the sympathetic activation may also cause other debilitating symptoms of POTS, such as anxiety, insomnia, and GI dysmotility. Although POTS symptoms may appear diverse, they can be clustered into vasomotor and sympathetic symptoms as shown in Fig. 1. In the emergency setting, it is important to understand that POTS patients present with various non-cardiac symptoms, in addition to tachycardia and OI. Furthermore, a study showed that POTS patients visit the ED much less frequently after diagnosis [30]. Therefore, suspecting POTS in the ED is crucial for referring patients to appropriate care in a timely manner.

Notably, typical symptoms of PASC are almost identical to those of POTS, and most can be clustered into vasomotor and sympathetic symptoms. From the cases we reviewed, no specific symptoms were exclusively observed in PASC or POTS, except loss of smell was unique to PASC. Although most patients with loss of smell make a full recovery within one year, a small percentage of patients develop permanent loss of smell [32]. Therefore, hypothetically, PASC syndrome occurs because of autonomic nerve dysfunction, particularly in peripheral sympathetic vasomotor fibers. To support this hypothesis, evidence of sudomotor or small

![Fig. 1. Postural orthostatic tachycardia syndrome (POTS) symptom cluster. POTS symptoms can be divided into sympathetic vasomotor dysfunction and sympathetic overcompensation. Because POTS patients experience symptoms of both sympathetic dysfunction and sympathetic hyperfunction, medications should be used with caution. For example, β-blockers can improve tachycardia and anxiety but worsen orthostatic intolerance and fatigue.](image-url)
fiber neuropathy in PASC has been increasingly observed in recent studies [33,34]. Sudomotor fibers branch off directly from sympathetic chain ganglia, and impairment of sudomotor fibers can indicate sympathetic nerve dysfunction and subsequent vasomotor dysfunction. Sudomotor function can be evaluated in several ways. As reported by Park et al. [27], the patient with PASC showed reduced QSART, indicating peripheral sympathetic dysfunction. In addition, sudomotor innervation can be quantified using immunohistochemistry staining with PGP9.5 on a cutaneous nerve biopsy [35]. However, direct comparison of sudomotor fiber density between patients with PASC and normal controls has not been performed. Because sympathetic nerve fibers are unmyelinated small fibers, neuropathy can indirectly indicate sympathetic vasomotor dysfunction.

Notably, not all PASC patients who received autonomic testing or active standing test met the criteria for POTS. Autonomic testing showed various cardiovascular responses, including OH, vasovagal syncope, and OI, although these patients presented with similar symptoms and signs. Several explanations are possible. First, diagnosis of POTS was inconsistent among studies. POTS is typically diagnosed based on the HUTT or active standing test. In the active standing test, muscle contraction from gastrocnemius muscles increases cardiac preload, potentially masquerading as orthostatic tachycardia. Plash et al. [36] showed that differences in heart rate during the active standing test are significantly smaller compared with those of the HUTT and suggested that diagnosis of POTS should not be based solely on orthostatic tachycardia. However, consensus is lacking on a specific modality for diagnosing POTS. Second, PASC can possibly affect certain levels of sympathetic vasomotor function, causing specific symptoms, and POTS only occurs when certain areas of sympathetic ganglia are affected. For example, if sympathetic vasomotor function is primarily impaired in splanchnic vasculature, PASC can present predominantly as GI symptoms but not meet the criteria for POTS. Novak et al. [33] recently showed significant reduction of cerebral circulation during the HUTT in PASC patients although their heart rate changes did not meet the criteria for POTS. Therefore, PASC patients with vasomotor symptoms may share the same underlying pathophysiology whether or not they meet the criteria for POTS. Third, symptoms change over time in POTS. In particular, cardiac symptoms, such as palpitation and lightheadedness, usually resolve over time as other symptoms, such as chronic fatigue, brain fog, and GI symptoms, emerge. Considering that the COVID-19 pandemic started approximately 3 years ago, response to the HUTT may change over time in PASC patients in the next several years.

We also found three case reports of POTS after COVID-19 vacci-

cination. Although causality between POTS and vaccines cannot be inferred from these cases, some vaccines are associated with various autoimmune neurological diseases such as Guillain–Barre syndrome or multiple sclerosis [37]. Molecular mimicry between microbial agents and the human host hypothetically plays a role in the development of autoimmunity. In the three cases of post-vaccination POTS, the symptoms and signs were almost identical to those of PASC, indicating that COVID-19 vaccines share the same target autoantibody epitope with PASC presenting as immune-mediated POTS. However, this should not discourage patients from receiving vaccines. On the contrary, COVID-19 vaccines can potentially prevent PASC because COVID-19 infection is more likely to cause PASC, and COVID-19 vaccines are proven protective against SARS-CoV-2 virus.

Currently, there are no treatments for post-COVID-19 POTS that target sympathetic vasomotor nerve, although a few clinical trials are testing various immune-modulating agents for post-COVID-19 POTS. The main treatment for post-COVID-19 POTS is volume expansion to increase cardiac preload. Various strategies exist to achieve volume expansion in POTS patients. First, patients are instructed to increase water and sodium intake. The standard amount of water and sodium recommended for POTS patients has not been established; however, in many clinics, patients are recommended to drink 2 to 4 L of water and ingest 3 to 4 g of sodium per day. To achieve volume expansion, consuming water and sodium as fast as possible is also important. Second, certain medications can be used to facilitate volume expansion. Fludrocortisone or α1 agonists, such as midodrine, can improve vasomotor symptoms including brain fog and OI. Stimulants (e.g., methylphenidate) are frequently used for brain fog and fatigue but should be used with caution because they can worsen sympathetic symptoms such as insomnia or palpitations. Third, graded cardiopulmonary training can significantly enhance blood volume over an extended period. However, it is important to understand that patients with POTS have difficulty tolerating exercise due to vasomotor dysregulation as they often develop postexercise flare or postexercise malaise if they overexert themselves. Therefore, slowly advancing their exercise capacity over a long period of time is critical. Last, if POTS is suspected in the ED, an active standing test can be performed to identify orthostatic tachycardia, assuming the patient’s cardiac functions are normal. For acute volume expansion in the ED, a bolus infusion of intravenous normal saline can be delivered to improve the symptoms of POTS. In addition, a short-acting α1 agonist, such as midodrine or fludrocortisone, can be used to optimize volume expansion in conjunction with aggressive hydration.

As the COVID-19 pandemic continues into its 3rd year, PASC is
emerging as a global health threat. An increasing need exists for better clinical phenotyping and studying pathophysiology of PASC. However, recognizing certain PASC subtypes, such as POTS, in an emergency setting is important because treatments are available for POTS.

**CONFLICT OF INTEREST**

No potential conflict of interest relevant to this article was reported.

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None.

**AUTHOR CONTRIBUTIONS**

Conceptualization: all authors; Data curation: all authors; Methodology: all authors; Visualization: SD; Supervision: TC; Writing–original draft: SD; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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**REFERENCES**

Predicting in-hospital mortality in pulmonary embolism patients: development and external validation of the PATHOS score

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Objective According to the 2019 European Society of Cardiology (ESC) guidelines on pulmonary embolism (PE), prognosis is calculated using the Pulmonary Embolism Severity Index (PESI), a complex score with debated validity, or simplified PESI (sPESI). We have developed and validated a new risk score for in-hospital mortality (IHM) of patients with PE in the emergency department.

Methods This retrospective, dual-center cohort study was conducted in the emergency departments of two third-level university hospitals. Patients aged > 18 years with a contrast-enhanced computed tomography-confirmed PE were included. Clinical variables and laboratory tests were evaluated blindly to IHM. Multivariable logistic regression was performed to identify the new score’s predictors, and the new score was compared with the PESI, sPESI, and shock index.

Results A total of 1,358 patients were included in this study: 586 in the derivation cohort and 772 in the validation cohort, with a global 10.6% of IHM. The PATHOS scores were developed using independent variables to predict mortality: platelet count, age, troponin, heart rate, oxygenation, and systolic blood pressure. The PATHOS score showed good calibration and high discrimination, with an area under the receiver operating characteristics curve of 0.83 (95% confidence interval [CI], 0.77–0.89) in the derivation population and 0.74 (95% CI, 0.68–0.80) in the validation cohort, which is significantly higher than the PESI, sPESI, and shock index in both cohorts (P < 0.01 for all comparisons).

Conclusion PATHOS is a simple and effective prognostic score for predicting IHM in patients with PE in an emergency setting.

Keywords Pulmonary embolism; Prognosis; Clinical prediction rules; Emergency medical services
INTRODUCTION

Pulmonary embolism (PE) is the migration of solid material through the bloodstream to the pulmonary circulation. PE is one of the leading causes of mortality in the USA and Europe, causing approximately 300,000 deaths per year in the USA [1]. PE has a complex pathophysiology: the occlusion of 30% to 50% of the total cross-sectional area of the pulmonary arterial bed causes a significant increase in pulmonary artery pressure and acute right ventricular (RV) afterloads [2]. An acute RV afterload leads to decreased RV and cardiac output, which is potentially responsible for obstructive shock, while pulmonary circulation worsens the exchange of oxygen due to a ventilation-perfusion mismatch [3]. However, the extent of pulmonary arterial bed involvement is highly variable, and the same clot migration could have different effects on pulmonary and systemic circulation depending on each patient’s cardiac and pulmonary status. Therefore, the symptoms, clinical signs, and laboratory data can be highly variable, but a timely diagnosis and prognostic assessment are nonetheless essential for correct management of this condition.

The most recent guidelines on PE were published in 2020 by the European Society of Cardiology (ESC) and recommend the use of a diagnostic and therapeutic strategy based on the predicted risk of either PE or short-term mortality. Patients with hemodynamic instability are at higher risk of early mortality, and patients without hemodynamic instability need further risk stratification according to the Pulmonary Embolism Severity Index (PESI), simplified PESI, and shock index in predicting in-hospital mortality among patients with pulmonary embolism. It had an area under the receiver operating characteristics curve of 0.778 (95% confidence interval, 0.728–0.810), high calibration, and an ability to identify patients with 1.8% to 85.0% chances of in-hospital mortality.

METHODS

Ethical statements
This study was conducted in accordance with the Declaration of Helsinki and approved by the Central Emilia Wide Area Ethical Committee of the Emilia-Romagna Region (CE-AVEC; No. 149/2022/ Oss/AOUFe). Informed consent was waived due to the study’s retrospective nature. The TRIPOD (transparent reporting of a multivariable prediction model for individual prognosis or diagnosis) statement [8] has been followed in preparing this manuscript (Supplementary Material 1).

Study design
This retrospective observational study was conducted in the EDs of two third-level university hospitals, each with more than 80,000 patient visits per year. The two EDs are in very different geographic locations.
areas with equally different demographic and sociocultural characteristics: a large, industrialized metropolis of almost 3 million people in central Italy and a city in northern Italy serving an area of 350,000 inhabitants. Both institutions are referral centers for cardiopulmonary emergencies in their respective districts. Clinical data were collected by analyzing the hospital data systems for vital signs, laboratory data, and demographic data. The clinical data used are those presented upon arrival in the ED. All variables are entered into the new model as dichotomous variables; for continuous variables, the best cutoff was identified as the one with the highest Youden index. The already proposed cutoff was maintained unless it differed clinically from the value with the highest Youden index. Platelet count was evaluated as abnormal when it was < 100 or > 400x10^3/μL, as already proposed [9]. Different troponin determination techniques have been used over time in the two hospitals with the following normal upper limits: (1) high sensitivity cardiac–Troponin I (hs-cTnI) < 20 and < 12 ng/L for male and female patients, respectively, in the derivation cohort in the years 2018–2021; and (2) hs-cTnI with a normal range of 0.04 ng/mL in the years 2018–2020 and hs-cTnI with a normal range of < 57 and < 37 ng/L for male and female patients, respectively, from May 3, 2020, to December 2021 in the validation cohort. Therefore, we decided to report the troponin levels only as above the normal limit provided by the laboratory for the given determination. Altered mental status was defined as the occurrence of disorientation, lethargy, stupor, or coma upon admission to the ED. PESI and sPESI were calculated for each patient according to the 2019 ESC guidelines on PE [4], and the SI was calculated as heart rate/systolic blood pressure and considered to be positive at values > 0.7 (see Table 1 for score calculation).

IHM was reported as all-cause in-hospital death following admission, regardless of the length of in-hospital stay (LoS). The occurrence of IHM and LoS were both evaluated by a second investigator, who checked the information system blinded to other clinical data. IHM was reported as secondary to all causes of in-hospital death.

**Study patients and enrollment criteria**

All patients aged > 18 years evaluated in the ED for acute PE as the main diagnosis from January 1, 2018 to May 30, 2021 were included. Patients with PE diagnoses were retrieved using a computerized search of ED discharge codes. The patients whose diagnosis of PE had been made using contrast chest CT were included in the study cohort.

Patients who were pregnant, did not receive a PE diagnosis in the ED, or had an inconsistent or incomplete set of data for calculating the evaluated scores were excluded from the final analysis.

**Table 1. Prognostic scores assessed in the derivation and validation cohorts under investigation**

<table>
<thead>
<tr>
<th>Score</th>
<th>Point</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PESI</strong></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>+1/yr</td>
</tr>
<tr>
<td>Male sex</td>
<td>+10</td>
</tr>
<tr>
<td>History of cancer</td>
<td>+30</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>+10</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>+10</td>
</tr>
<tr>
<td>HR &gt; 110 ppm</td>
<td>+20</td>
</tr>
<tr>
<td>SBP &lt; 100 mmHg</td>
<td>+30</td>
</tr>
<tr>
<td>Respiratory rate &gt; 30 breaths/min</td>
<td>+20</td>
</tr>
<tr>
<td>Temperature &lt; 36 °C</td>
<td>+20</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>+60</td>
</tr>
<tr>
<td>sPESI</td>
<td></td>
</tr>
<tr>
<td>Age &gt; 80 yr</td>
<td>+1</td>
</tr>
<tr>
<td>History of cancer</td>
<td>+1</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>+1</td>
</tr>
<tr>
<td>HR &gt; 110 ppm</td>
<td>+1</td>
</tr>
<tr>
<td>SBP &lt; 100 mmHg</td>
<td>+1</td>
</tr>
<tr>
<td>SpO₂ &lt; 90%</td>
<td>+20</td>
</tr>
<tr>
<td><strong>sPATHOS score</strong></td>
<td></td>
</tr>
<tr>
<td>Platelet count &lt; 100 or &gt; 400x10^3/μL</td>
<td>+1</td>
</tr>
<tr>
<td>Age &gt; 80 yr</td>
<td>+1</td>
</tr>
<tr>
<td>Troponin level &gt; cutoff</td>
<td>+1</td>
</tr>
<tr>
<td>HR &gt; 100 ppm</td>
<td>+1</td>
</tr>
<tr>
<td>SpO₂ &lt; 90%</td>
<td>+1</td>
</tr>
<tr>
<td>SBP &lt; 100 mmHg</td>
<td>+1</td>
</tr>
</tbody>
</table>

**Score derivation**

To build a new prognostic score, we randomly chose one ED as the derivation cohort. We performed univariate regression analyses to identify predictors of IHM. Among those predictors, only items identified as independent predictors in the multivariable regression analysis were included in the final logistic model. To assign a value to each of the included variables, we created a simple linear regression model containing all the predictors, and points were attributed to each variable by considering the adjusted standardized coefficients of each item. The model was checked for multicollinearity via variance inflation factor analysis [10]. The internal validity of the score was confirmed using bootstrap analysis [11].

**Score validation**

ED patients in the other hospital were enrolled as the validation cohort. Clinical charts were retrospectively analyzed to extract the
clinical data required to compute the PESI, sPESI, SI, new prognostic score, and IHM. The clinical data were extracted blindly to IHM, and all scores were calculated as reported in Table 1. The calibration and discrimination of the new score were assessed, and its diagnostic accuracy was compared with that of the PESI, sPESI, and SI. A multivariable logistic regression analysis was performed for each score to assess the predictive value of each item in terms of odds ratios (ORs) and 95% confidence interval (CIs).

Statistical analysis

Normally distributed data are described as the mean ± standard deviation; non-normally distributed data are described as the median and interquartile range; and categorical data are reported as absolute numbers and percentages. Normally distributed data were compared via independent sample t-testing or Welch t-testing in cases of unequal variance between groups. Non-normally distributed data were compared via the Mann-Whitney U-test. The Pearson chi-square test was used to compare categorical dependent variables among at least two independent groups. Missing data not essential for score calculation were imputed via regression multiple imputation analysis [12].

The discrimination ability of each score was evaluated via the AUROC. The AUROCs of the scores were compared via the DeLong test [13] in the derivation, validation, and global cohorts. The best cutoff was identified according to the highest Youden index [14]. The category-based net reclassification improvement (NRI) was calculated according to Leening et al. [15] to evaluate the difference in risk stratification between the developed score and the PESI and sPESI. The newly developed score was compared to the five risk categories of the PESI (class I, < 65; class II, 66–85; class III, 86–105; class IV, 106–125; and class V, > 125) according to the ESC 2019 guidelines [4]. The newly developed score was compared to the sPESI by identifying a low-risk class for predicted IHM < 5% and a high-risk class for predicted IHM > 5%. The event NRI, non-event NRI, and overall NRI are reported for each comparison. Calibration of the developed model was assessed via the Hosmer-Lemeshow test in the derivation and validation groups [16].

Statistical analyses were performed using IBM SPSS ver. 25 (IBM Corp) and MedCalc ver. 17.6 (MedCalc Software).

RESULTS

During the study period, 2,117 patients were admitted for PE or suspected PE: 998 in the derivation cohort and 1,119 in the validation cohort. However, 307 and 251 patients were excluded from the derivation and validation cohorts, respectively, for incomplete data. One hundred and five patients from the derivation cohort and 92 patients from the validation cohort were excluded because of non-confirmed PE, and four patients from the validation cohort were excluded due to pregnancy (Fig. 1). Therefore, 1,358 patients were included in the study: 586 in the derivation cohort and 772 in the validation cohort. The patients had a mean age of...
69.88 years, and 44.2% of them were male, with a median LoS of 7.5 days (interquartile range, 4.3–13.0 days). Overall, 10.5% of the included patients died in the hospital (10.2% in the derivation group and 10.6% in the validation group, P = 0.818). Compared with the derivation cohort, the validation cohort was younger and presented to the ED with a higher respiratory rate, heart rate (HR), peripheral oxygen saturation (SpO₂), and body temperature; lower systolic blood pressure (SBP); and less-frequent altered mental status. According to the lab values, the validation population presented with a higher platelet count and a higher rate of troponin above the given cutoff value. Patients in the validation cohort had a more frequent history of cancer, lower PESI and higher SI scores, and no difference in the sPESI and PATHOS (platelets, age, troponin, HR, oxygenation, and SBP) scores from patients in the derivation cohort. The LoS was higher in the validation population, with no difference in terms of IHM between the groups (Table 2). Patients with IHM were older and had lower SpO₂, SBP, and diastolic BP; higher HR; a higher frequency of altered mental status, troponin value > cutoff, and abnormal platelet count; and higher PESI, sPESI, SI, and PATHOS scores than those who survived to discharge in both the derivation and validation cohorts (Table 3).

Among all the variables identified as potential predictors in the derivation cohort (Table 3), only HR demonstrated a different better cutoff than the previously published value (100 pulses per minute [ppm] instead of 110 ppm). In the end, platelet count < 100 or > 400 × 10³/μL, age > 80 years, troponin > the given cutoff, HR > 100 ppm, SpO₂ < 90%, and SBP < 100 mmHg were identified as independent predictors in the multivariable logistic regression and included in the PATHOS score (Tables 1, 4). All PATHOS score items were also shown to be independent predictors in the validation cohort, whereas only three of the 11 PESI items (HR, P-value

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 1,358)</th>
<th>Derivation cohort (n = 586)</th>
<th>Validation cohort (n = 772)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>600 (44.2)</td>
<td>253 (43.2)</td>
<td>347 (44.9)</td>
<td>0.514</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>69.88 ± 14.89</td>
<td>73.62 ± 15.00</td>
<td>69.54 ± 14.00</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>&gt; 80</td>
<td>456 (33.6)</td>
<td>243 (41.5)</td>
<td>213 (27.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Respiratory rate (ppm)</td>
<td>25.2 ± 5.6</td>
<td>20.8 ± 6.6</td>
<td>25.6 ± 5.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>&gt; 30</td>
<td>235 (17.3)</td>
<td>16 (2.7)</td>
<td>219 (28.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SpO₂ (%)</td>
<td>95 (92–98)</td>
<td>94 (91–98)</td>
<td>95 (92–97)</td>
<td>0.947</td>
</tr>
<tr>
<td>&lt; 90</td>
<td>252 (18.6)</td>
<td>131 (22.4)</td>
<td>121 (15.4)</td>
<td>0.010</td>
</tr>
<tr>
<td>Heart rate (ppm)</td>
<td>96 ± 19</td>
<td>93 ± 21</td>
<td>96 ± 19</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>&gt; 100</td>
<td>517 (38.1)</td>
<td>180 (30.7)</td>
<td>337 (43.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>&gt; 110</td>
<td>310 (22.8)</td>
<td>104 (17.7)</td>
<td>206 (26.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>130 ± 24</td>
<td>139 ± 26</td>
<td>128 ± 23</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>&lt; 100</td>
<td>177 (13.0)</td>
<td>88 (15.0)</td>
<td>89 (11.5)</td>
<td>0.010</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>79.5 ± 15.9</td>
<td>80.0 ± 15.0</td>
<td>79.4 ± 15.0</td>
<td>0.010</td>
</tr>
<tr>
<td>Body temperature (°C)</td>
<td>37.05 ± 0.76</td>
<td>36.50 ± 0.78</td>
<td>37.10 ± 0.74</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>&lt; 36</td>
<td>15 (1.1)</td>
<td>2 (0.3)</td>
<td>13 (1.7)</td>
<td>0.231</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>125 (9.2)</td>
<td>89 (15.2)</td>
<td>36 (4.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Troponin &gt; cutoff</td>
<td>608 (44.8)</td>
<td>202 (34.5)</td>
<td>312 (40.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Platelets (×10³/μL)</td>
<td>261 ± 129</td>
<td>222 ± 77</td>
<td>265 ± 133</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>&lt; 100 or &gt; 400</td>
<td>191 (14.1)</td>
<td>54 (9.2)</td>
<td>137 (17.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>History of cancer</td>
<td>477 (35.1)</td>
<td>170 (29.0)</td>
<td>307 (39.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>127 (9.4)</td>
<td>61 (10.4)</td>
<td>66 (8.5)</td>
<td>0.212</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>133 (9.8)</td>
<td>67 (11.4)</td>
<td>66 (8.5)</td>
<td>0.063</td>
</tr>
<tr>
<td>PESI</td>
<td>101 ± 33</td>
<td>116 ± 47</td>
<td>100 ± 31</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>sPESI</td>
<td>1.42 ± 1</td>
<td>1.33 ± 1</td>
<td>1.43 ± 1</td>
<td>0.570</td>
</tr>
<tr>
<td>Shock index</td>
<td>0.76 ± 0.22</td>
<td>0.70 ± 0.20</td>
<td>0.77 ± 0.22</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>&gt; 0.7</td>
<td>649 (47.8)</td>
<td>206 (35.2)</td>
<td>443 (57.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PATHOS score</td>
<td>1.68 ± 1.17</td>
<td>1.63 ± 1.23</td>
<td>1.56 ± 1.11</td>
<td>0.490</td>
</tr>
<tr>
<td>Length of stay (day)</td>
<td>7.5 (4.3–13.0)</td>
<td>6.0 (3.0–11.0)</td>
<td>8.3 (5.3–14.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>In-hospital death</td>
<td>142 (10.5)</td>
<td>60 (10.2)</td>
<td>82 (10.6)</td>
<td>0.818</td>
</tr>
</tbody>
</table>

Values are presented as number (%), mean ± standard deviation, or median (interquartile range). ppm, pulses per minute; SpO₂, peripheral oxygen saturation; SBP, systolic blood pressure; DBP, diastolic blood pressure; PESI, Pulmonary Embolism Severity Index; sPESI, simplified Pulmonary Embolism Severity Index; PATHOS, platelets, age, troponin, heart rate, peripheral oxygen saturation, and systolic blood pressure.

Table 2. Comparison of demographic and clinical features between the derivation and validation cohorts
SBP, and SpO₂) were independent predictors in both groups, with age and altered mental status found to be independent predictors only in the validation group. Among the sPESI items, a history of cancer was not an independent predictor in the derivation cohort, and chronic heart failure was not an independent predictor in either cohort (Table 4).

The linear regression model analysis of the PATHOS score showed a B standardized coefficient equal to 0.162 (P = 0.001) for platelet count < 100 or > 400 × 10⁹/μL, 0.103 (P = 0.038) for age > 80 years, 0.112 (P = 0.031) for troponin > the cutoff, 0.131 (P = 0.010) for HR > 100 ppm, 0.145 (P = 0.005) for SpO₂ < 90%, and 0.178 (P < 0.001) for SBP < 100 mmHg. Therefore, one point was assigned to each item. Moreover, each item showed a variance inflation factor of < 2.001, excluding multicollinearity.

The PATHOS score showed good calibration, with a Hosmer-Lemeshow χ² = 6.15 and P = 0.52 in the derivation group and χ² = 1.63 and P = 0.977 in the validation group. In the derivation group, the PATHOS score had the highest global accuracy, with an AUROC of 0.827 (95% CI, 0.769–0.885), which was significantly higher than that of the PESI (AUROC, 0.786; 95% CI, 0.72–0.85; P < 0.01), sPESI (AUROC, 0.791; 95% CI, 0.726–0.856; P = 0.01), and SI (AUROC, 0.64; 95% CI, 0.543–0.750; P < 0.001) (Fig. 2).

When applied to the validation group, the PATHOS score had an AUROC of 0.74 (95% CI, 0.68–0.80), which was also significantly higher than that of the PESI (AUROC, 0.68; 95% CI, 0.61–0.74; P = 0.013), with no difference between the PESI and sPESI (AUROC, 0.71; 95% CI, 0.64–0.77; P = 0.24) or between the PESI and SI (AUROC, 0.67; 95% CI, 0.61–0.74; P = 0.94) (Fig. 3). In the global cohort, a PATHOS score > 0 showed a negative predictive value of 98.9 and a negative likelihood ratio of 0.09; whereas a
### Table 4. Characteristics of the analyzed prognostic scores: multivariable logistic regression analysis for in-hospital death

<table>
<thead>
<tr>
<th>Variable</th>
<th>Derivation cohort</th>
<th>Validation cohort</th>
<th>Derivation cohort</th>
<th>Validation cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P-value</td>
<td>OR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td><strong>PESI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>1.03 (0.99–1.07)</td>
<td>0.110</td>
<td>1.03 (1.01–1.05)</td>
<td>&lt; 0.010</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.73 (0.28–1.86)</td>
<td>0.510</td>
<td>0.98 (0.60–1.60)</td>
<td>0.950</td>
</tr>
<tr>
<td>History of cancer</td>
<td>1.08 (0.56–2.08)</td>
<td>0.810</td>
<td>1.46 (0.99–2.16)</td>
<td>0.530</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>0.65 (0.19–2.26)</td>
<td>0.500</td>
<td>1.58 (0.75–3.33)</td>
<td>0.220</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>1.48 (0.47–4.62)</td>
<td>0.490</td>
<td>0.41 (0.15–1.12)</td>
<td>0.840</td>
</tr>
<tr>
<td>HR &gt; 110 ppm</td>
<td>4.48 (7.18–11.28)</td>
<td>&lt; 0.010</td>
<td>1.93 (1.14–3.27)</td>
<td>0.014</td>
</tr>
<tr>
<td>SBP &lt; 100 mmHg</td>
<td>8.22 (3.47–22.48)</td>
<td>&lt; 0.010</td>
<td>2.39 (1.30–4.17)</td>
<td>&lt; 0.010</td>
</tr>
<tr>
<td>Respiratory rate &gt; 30 ppm</td>
<td>3.56 (0.67–19.1)</td>
<td>0.299</td>
<td>1.26 (0.78–2.01)</td>
<td>0.860</td>
</tr>
<tr>
<td>Temperature &lt; 36 °C</td>
<td>0.89 (0.42–1.87)</td>
<td>0.760</td>
<td>0.56 (0.06–4.73)</td>
<td>0.590</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>1.72 (0.66–4.47)</td>
<td>0.690</td>
<td>2.38 (1.02–5.51)</td>
<td>0.030</td>
</tr>
<tr>
<td>SpO&lt;sub&gt;2&lt;/sub&gt; &lt; 90%</td>
<td>3.21 (1.31–7.84)</td>
<td>&lt; 0.010</td>
<td>2.43 (1.40–4.20)</td>
<td>&lt; 0.010</td>
</tr>
<tr>
<td><strong>sPESI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt; 80 yr</td>
<td>2.36 (1.24–4.52)</td>
<td>0.015</td>
<td>3.00 (1.81–4.97)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>History of cancer</td>
<td>1.30 (0.76–2.69)</td>
<td>0.260</td>
<td>1.70 (0.49–6.63)</td>
<td>0.400</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>1.10 (0.45–2.63)</td>
<td>0.630</td>
<td>1.38 (0.65–2.92)</td>
<td>0.400</td>
</tr>
<tr>
<td>HR &gt; 110 ppm</td>
<td>2.04 (1.10–4.80)</td>
<td>&lt; 0.010</td>
<td>1.93 (1.25–3.41)</td>
<td>&gt; 0.010</td>
</tr>
<tr>
<td>SBP &lt; 100 mmHg</td>
<td>4.24 (2.17–8.20)</td>
<td>&lt; 0.010</td>
<td>2.92 (1.62–5.25)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SpO&lt;sub&gt;2&lt;/sub&gt; &lt; 90%</td>
<td>3.69 (2.00–6.74)</td>
<td>&lt; 0.010</td>
<td>2.47 (1.44–4.23)</td>
<td>&lt; 0.010</td>
</tr>
<tr>
<td><strong>PATHOS score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count &lt; 100 or &gt; 400 × 10&lt;sup&gt;3&lt;/sup&gt;/μL</td>
<td>4.62 (1.60–14.11)</td>
<td>&lt; 0.010</td>
<td>2.68 (1.55–4.62)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Age &gt; 80 yr</td>
<td>2.34 (1.15–4.75)</td>
<td>0.020</td>
<td>3.07 (1.85–5.10)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Troponin level &gt; cutoff</td>
<td>2.56 (1.10–6.10)</td>
<td>0.030</td>
<td>1.78 (1.15–2.70)</td>
<td>0.020</td>
</tr>
<tr>
<td>HR &gt; 110 ppm</td>
<td>2.90 (1.30–6.00)</td>
<td>&lt; 0.010</td>
<td>1.84 (1.10–3.05)</td>
<td>0.018</td>
</tr>
<tr>
<td>SBP &lt; 100 mmHg</td>
<td>2.16 (1.06–4.41)</td>
<td>0.030</td>
<td>2.40 (1.40–4.16)</td>
<td>0.002</td>
</tr>
<tr>
<td>SpO&lt;sub&gt;2&lt;/sub&gt; &lt; 90%</td>
<td>4.98 (2.27–9.09)</td>
<td>&lt; 0.010</td>
<td>2.54 (1.40–4.60)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval; PESI, Pulmonary Embolism Severity Index; HR, heart rate; ppm, pulses per minute; SBP, systolic blood pressure; SpO<sub>2</sub>, peripheral oxygen saturation; sPESI, simplified Pulmonary Embolism Severity Index; PATHOS, platelets, age, troponin, heart rate, peripheral oxygen saturation, and systolic blood pressure.

### Table 5. Characteristics of the PATHOS score in the whole cohort

<table>
<thead>
<tr>
<th>Total score</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>+LR (95% CI)</th>
<th>−LR (95% CI)</th>
<th>PPV</th>
<th>NPV</th>
<th>IHM probability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>98.44 (94.5–99.8)</td>
<td>17.24 (15.0–19.7)</td>
<td>1.19 (1.0–1.4)</td>
<td>0.091 (0.02–0.4)</td>
<td>13.1</td>
<td>98.9</td>
<td>1.8</td>
</tr>
<tr>
<td>1</td>
<td>86.72 (79.6–92.1)</td>
<td>50.94 (47.8–54.1)</td>
<td>1.77 (1.6–1.9)</td>
<td>0.26 (0.2–0.4)</td>
<td>18.3</td>
<td>96.8</td>
<td>3–6</td>
</tr>
<tr>
<td>2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>60.94 (51.9–69.4)</td>
<td>81.67 (79.1–84.0)</td>
<td>3.32 (2.9–3.8)</td>
<td>0.48 (0.4–0.6)</td>
<td>29.7</td>
<td>94.3</td>
<td>6–15</td>
</tr>
<tr>
<td>3</td>
<td>31.25 (23.4–40.0)</td>
<td>94.15 (92.5–95.5)</td>
<td>5.34 (4.1–6.9)</td>
<td>0.73 (0.6–1.0)</td>
<td>40.4</td>
<td>91.5</td>
<td>15–34</td>
</tr>
<tr>
<td>4</td>
<td>6.25 (2.7–11.9)</td>
<td>99.11 (98.3–99.6)</td>
<td>7.01 (3.6–13.7)</td>
<td>0.95 (0.5–1.8)</td>
<td>47.1</td>
<td>89.3</td>
<td>32–60</td>
</tr>
<tr>
<td>5</td>
<td>0 (0–2.8)</td>
<td>99.90 (99.4–100)</td>
<td>1.00 (0.1–7.1)</td>
<td>0</td>
<td>88.7</td>
<td>60–74</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0 (0–2.8)</td>
<td>100 (99.6–100)</td>
<td>-</td>
<td>1.00</td>
<td>-</td>
<td>88.7</td>
<td>85</td>
</tr>
</tbody>
</table>

PATHOS score consists of platelets < 100 or > 400 × 10<sup>3</sup>/μL, age > 80 years, troponin > cutoff, heart rate > 100 ppm, peripheral oxygen saturation < 90%, and systolic blood pressure < 100 mmHg. The predicted probability of IHM can be calculated as follows: P = 1/[1 + exp{−(−3.98 + 1.17 × platelet count + 0.99 × age > 80 years + 0.56 × troponin level > cutoff + 0.76 × heart rate > 100 ppm + 0.94 × peripheral oxygen saturation < 90% + 1.17 × systolic blood pressure < 100 mmHg)}] × 100 (interceptor, −3.98; standard error, 0.23).

PATHOS, platelets, age, troponin, heart rate, peripheral oxygen saturation, and systolic blood pressure; CI, confidence interval; LR, likelihood ratio; PPV, positive predictive value; NPV, negative predictive value; IHM, in-hospital mortality.

<sup>a</sup>Best cutoff according to the Youden index.

PATHOS score > 4 showed a positive predictive value equal to 47% with a positive likelihood ratio of 7. The best cutoff is a PATHOS score > 2, which had 60% sensitivity, 81% specificity, a 3.3 likelihood ratio, 30% positive predictive value, and 94% negative predictive value. Moreover, a PATHOS score of 0 is associated with an all-cause IHM risk of 1.8%, a PATHOS score of 6 to IHM risk of 85%, and scores of 2 to 5 are progressively associated with different probabilities due to the slightly different risks associated...
with each predictor (Table 5).

As illustrated in Table 5, seven IHM risk classes were identified for the PATHOS score (range, 0–6). Comparing the PATHOS score with the PESI, the event NRI was −0.09, the non-event NRI was 0.31, and the overall NRI was 0.22. To compare the PATHOS score with the sPESI, a low risk of IHM was defined as PATHOS 0 to 1 and high risk of IHM as PATHOS > 1. Comparing those two PATHOS score risk classes with the sPESI, the event NRI was −0.08, the non-event NRI was 0.29, and the overall NRI was 0.21.

DISCUSSION

Risk stratification, along with the prompt diagnosis and stabilization of critically ill patients, remains a cornerstone of an emergency physician’s daily practice. Predicting which patients have a high or low risk of adverse events determines the most appropriate setting for patients and appropriate resource allocation. The PESI is a complex score that uses 11 clinical parameters to calculate the risk of all-cause 30-day and 6-month mortality [17]. The complexity of the PESI leads to high interoperator variability among users [18,19] and a lower propensity to use it in clinical practice [20,21]. Although PE can significantly affect morbidity and mortality, not every 30-day mortality event is likely to be caused by PE, and a higher 30-day or 6-month mortality risk might not necessarily reflect the short-term mortality risk or the need for intensive care. IHM is recognized as a strong outcome, and correct risk stratification is fundamental for choosing to admit patients to the hospital and determining the intensity of care needed. In this study, we evaluated the prognostic accuracy of the PESI, sPESI, and SI and validated a newly developed risk score for IHM among patients with suspected PE. As reported in Table 3, patients with IHM had worse vital signs and higher PESI, sPESI, and PATHOS scores in both cohorts. However, similar to the results of Jimenez et al. [22] and Vinson et al. [23], different clinical items in the PESI and sPESI, such as sex, respiratory rate, body temperature, history of cancer, and presence of a chronic pulmonary disease, did not appear to be related to IHM in either of our cohorts; thus, those items increased the complexity of calculating the PESI and sPESI scores without improving their accuracy [24–27]. In contrast, PATHOS is a simple, easy-to-remember, operator-independent metric that is based on fixed cutoff values and includes only clinical items significantly predictive of IHM. PATHOS demonstrated better diagnostic accuracy than PESI, sPESI, and SI in both the populations evaluated in this study (Figs. 2, 3). Notably, our two cohorts are very different in terms of demographic and clinical characteristics due to their different locations and resident popu-

Fig. 2. The receiver operating characteristic (ROC) curves of the included scores of the derivation cohort. The area under the ROC curve (AUROC) of the shock index is 0.64 (95% confidence interval [CI], 0.543–0.750), the AUROC of the simplified Pulmonary Embolism Severity Index (sPESI) is 0.791 (95% CI, 0.726–0.856), the AUROC of the PESI is 0.786 (95% CI, 0.720–0.850), the AUROC of the PATHOS (platelets, age, troponin, heart rate, oxygenation, and systolic blood pressure) score is 0.827 (95% CI, 0.769–0.885).

Fig. 3. The receiver operating characteristic (ROC) curves of the included scores of the validation cohort. The area under the ROC curve (AUROC) of the shock index is 0.67 (95% confidence interval [CI], 0.61–0.74), the AUROC of the simplified Pulmonary Embolism Severity Index (sPESI) is 0.71 (95% CI, 0.64–0.77), the AUROC of the PESI is 0.68 (95% CI, 0.61–0.74), the AUROC of the PATHOS (platelets, age, troponin, heart rate, oxygenation, and systolic blood pressure) score is 0.74 (95% CI, 0.68–0.80).
PATHOS score for PE in the ED

lations, so they reflect the actual variety of patients and the need for a simple and effective score in an emergency setting. Whereas the PESI and sPESI demonstrated the same limitations in our two unselected cohorts, PATHOS score is based on fundamental and easily available items to assess circulatory shock, pulmonary dysfunction, acute cardiac damage, and platelet count (the latter being an independent predictor of IHM in more conditions than just PE) [8,28–30]. According to our results, the positive overall NRIs in the comparisons between PATHOS and PESI and PATHOS and sPESI confirm that PATHOS has better discrimination accuracy than the older measures, showing that a net percentage of 31% (PATHOS vs. PESI) and 29% (PATHOS vs. sPESI) of patients without IHM were correctly reclassified by the new measure. Thus, compared with the other two scores, PATHOS has a higher ability to estimate patients at low risk for IHM than the PESI and sPESI. Moreover, the PATHOS score identified patients with very different risks of IHM with good calibration and the highest accuracy. As shown in Table 5, PATHOS identified patient subsets with low (score, 0–1; < 6%), moderate (score, 2–3; 6%–34%), and high risks (score, > 3; > 34%) of IHM. Moreover, because each clinical item has a slightly different prognostic value, we developed a regression equation (Table 5) to calculate the IHM risk based on the clinical features exhibited by each patient. Markers of cardiac dysfunction, such as those shown in ultrasonographic or chest CT evaluations of RV function, brain natriuretic peptide, or troponin [31–34], improve the stratification accuracy of clinical scores and are recommended for correct patient categorization [4]. Moreover, the inclusion of troponin in the clinical score has the advantage of underlining the importance of this biomarker, which could be a valid surrogate of RV dysfunction [35]. Therefore, the PATHOS score is a valuable tool to stratify patients even in settings with no prompt access to echocardiography.

As with any retrospective study, this study has limitations that should be acknowledged. The study cohort included only patients with CTPA-confirmed PE in the ED, which could have led to the exclusion of undiagnosed patients with PE, potentially leading to an incorrect estimation of the evaluated scores. Also, we did not include an echocardiographic or CTPA evaluation of RV dysfunction among the considered items; thus, we could not calculate the ESC risk class. Although that could reduce the risk stratification accuracy, we focused on clinical and easy-to-obtain laboratory parameters to increase the versatility of the new prognostic score in any ED setting. Moreover, due to the lack of generally accepted approaches for estimating the sample size needed for risk prediction models, we did not calculate a formal sample size. However, our study far exceeds the number of events needed for the six-item model developed; thus, it is expected to provide very robust estimates based on the recommended “rule of ten events per predictor” in multivariable logistic regression analyses [36]. Because the PESI and sPESI were derived and validated in large datasets [37], the possible superiority of PATHOS over the PESI and sPESI requires more evidence. Further studies are needed to indicate that PATHOS can be practically applied in daily clinical practice in an ED.

In conclusion, the new PATHOS measure incorporates elements of the ESC classification in a simple, unique score and should be useful for stratifying the risk of patients with PE in different ED settings. Although the PESI and ESC classification remain the most recommended risk stratification tools, PATHOS could turn out to be the easiest and most accurate score in daily ED clinical practice if it can be validated in further prospective cohorts.

SUPPLEMENTARY MATERIALS

Supplementary Material 1. TRIPOD (transparent reporting of a multivariable prediction model for individual prognosis or diagnosis) checklist: prediction model development and validation. Supplementary material is available at https://doi.org/10.15441/ceem.22.369.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

FUNDING

None.

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AUTHOR CONTRIBUTIONS

Conceptualization: MDS, MC, A Passaro, AG, RDG, FF; Data curation: MB, LDA, GG, ISF, TP, A Portoraro, MG, RP, GT; Formal anal-
sis: MDS, MC; Investigation: A Portoraro, AG, RDG, FF; Methodology: MDS, MC, A Passaro, AG, RDG, FF; Project administration: AG, RDG, FF; Resources: MDS, RP, A Passaro; Software: MDS, MC; Supervision: A Passaro, AG, RDG, FF; Validation: MDS, MC, A Passaro, AG, RDG, FF; Visualization: all authors; Writing–original draft: MDS, RDG, FF, MB, LDA, GG, ISF, TP, A Portoraro, MG; Writing–review & writing: all authors. All authors read and approved the final manuscript.

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Survival benefit of direct transport to trauma centers among patients with unintentional injuries in Korea: a propensity score-matched analysis

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Objective This study investigated the characteristics and survival rates of patients with unintentional severe trauma who visited a regional trauma center (TC) or a non-TC.

Methods This retrospective, national, population-based, observational, case-control study included patients with abnormal Revised Trauma Score from January 2018 to December 2018. We divided hospitals into two types, TC and non-TC, and compared several variables, including inhospital mortality. Propensity score matching was used to reduce the effect of confounding variables that influence survival outcome variables.

Results Of the 25,743 patients, 5,796 visited a TC and 19,947 visited a non-TC. Compared to patients treated at non-TCs, patients treated at TCs were more likely to have a higher Injury Severity Score (TC, 11.5; non-TC, 7.4; P < 0.001), higher rate of surgery or transcatheter arterial embolization (TC, 39.2%; non-TC, 17.6%; P < 0.001), and higher admission rate (TC, 64.7%; non-TC, 36.9%; P < 0.001) through the emergency department. After propensity score matching, 2,800 patients from both groups were analyzed. Patients in the TC had a higher survival rate than patients that were not treated in the TC (TC, 83.0%; non-TC, 78.6%; P = 0.003).

Conclusion This study using Korean emergency medical services data showed that initial transport to trauma centers was associated with mortality reduction. Further research is required because of limitations with use of single-year data and retrospective design.

Keywords Emergency medical services; Trauma centers; Propensity score; Hospital mortality

What is already known
Treatment of patients with severe trauma is resource-intensive and requires many human resources; thus, patients who need a higher level of care must be transported to an appropriate trauma center (TC). In the Korean emergency medical system, there is currently no distinction between regional TCs and non-TCs regarding transporting and treating major trauma patients.

What is new in the current study
The direct transport of patients with severe trauma to TCs was associated with better survival benefits than non-TCs. The time for surgery or transcatheter arterial embolization at TCs was shorter.
INTRODUCTION

Trauma is a leading cause of death in people under the age of 49 years, with more than 5 million patients dying each year from trauma [1]. Since trauma occurs more frequently in younger populations, it could negatively impact the labor market nationally [2]. Treatment for patients with severe trauma is resource-intensive; thus, patients who need higher levels of care should be transported to an appropriate trauma center (TC) [3].

Since the late 1960s, emergency medical services (EMS) have developed rapidly. The evolution of modern cardiopulmonary resuscitation and the recognition of motor vehicle crashes as one of the greatest public health problems in the United States have been well chronicled [4]. Most developed countries have established and implemented trauma delivery systems such as classification and transport of trauma patients from the prehospital stage. Consequently, the Korean government established a plan to design a national trauma system in 2012, with the main goal of establishing 17 TCs nationwide [5]. As of 2020, 17 TCs have been designated nationwide, and 15 have been officially opened and dedicated to treating patients with severe trauma. These centers receive annual financial support for dedicated personnel, along with government support for facilities and equipment [6].

The regional TC is a facility that allows a trauma team (traumatology, neurosurgery, and emergency medicine) to respond to patients within 10 minutes to provide integrated and essential treatment including resuscitation and initial treatment [7]. In the Korean emergency medical system, there are guidelines for transporting major trauma patients to TCs. But EMS has claimed that many of the major trauma patients who met the criteria for a TC were not transported appropriately due to unsupported conditions. At the non-TC, severe trauma patients who need a systematic response from the trauma team may receive inappropriately delayed initial treatment, such as emergency surgery or angiographic embolization [8].

In this study, we aimed to analyze the prognosis and related factors of patients with severe trauma by comparing the number of patients transported directly to regional TCs with those transported directly to non-TCs.

METHODS

Ethical statements

This study was approved by the Institutional Review Board of Kyung Hee University Hospital at Gangdong (No. KHNMC 2021-07-048). This study conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The requirement for informed consent was waived due to the retrospective nature of the study.

Study design and setting

This was a nationwide retrospective cohort study of Korean patients with severe injuries and multiple casualties transported by the Korean EMS. The study period was from January 2018 to December 2018.

The study included severe trauma patients with abnormal Revised Trauma Score (RTS) at the scene of the injury and who were transported to emergency departments (EDs) during the study period in Korea. Patients whose RTS was unknown, including those who experienced out-of-hospital cardiac arrest and were dead on arrival, were excluded. Patients with normal RTS, such as those who were transported due to nontraumatic causes or who had mild injuries and those with missing records, were not considered trauma patients and were excluded from the study. Intentional injuries, such as self-injury and suicide, were also excluded from the study. The Korean EMS is a single-tier, government-provided system, headed by the National Fire Agency, which provides basic life support ambulance services throughout the 17 provincial headquarters. All EMS providers can apply advanced airway support and can provide intravenous fluid to a patient following the EMS cardiopulmonary resuscitation protocol [9].

Clinical factors included the RTS and Injury Severity Score (ISS) as indicators to determine the degree of damage to individual patients. The RTS is a convenient tool for trauma triage and initial severity estimation. This physiological scoring system consists of the Glasgow Coma Scale, systolic blood pressure, and respiratory rate [10]. The ISS is the most widely used score to assess the extent of damage in patients with severe trauma in the hospital [11]. The ISS is based on the Abbreviated Injury Scale, which describes the severity of injury to different body parts (head, face, chest, abdomen, limb, and external), and the scores of the three most seriously damaged body parts are squared and summed to produce the ISS score [12]. The proportion of patients with ISS 16 or higher was used to compare injury severity.

Data collection and process

Patient data consisted of prehospital data acquired from the National Fire Agency and data confirmed through medical record surveys. Nonidentification measures were taken based on the Personal Information Protection Act and Statistics Act. According to the national statistics law, the Korea Disease Control and Prevention Agency dispatched trained medical record investigators to hospitals and collected hospital data by medical record review. An investigator in charge of community-based trauma status visited the medical institution confirmed by the 119 paramedic trans-
port information, checked whether it was a patient with severe injuries and multiple casualties, collected necessary information, and conducted an interfacility transfer investigation to confirm additional treatment and results. Trauma data consisted of sociodemographic information, injury information, progress during treatment, and results after hospitalization [13].

In this study, patients were assigned to either a TC or a non-TC. The outcome variable was in-hospital mortality, as reported in the nationwide trauma registry. The exposure variable of interest was whether a patient with ISS ≥ 16 received definitive trauma care, such as surgery or embolization at a designated TC or non-TC. In addition to the primary exposure variable (TC vs. non-TC), we considered multiple confounders, predictors, and effect modifiers for all multivariable outcome models: sex, injury mechanism (traffic-related, falls, stabbing or penetrating wound, burn, other), insurance, and interfacility transfer status [14].

**Statistical analysis**

Continuous variables are presented as means and standard deviations or medians and interquartile ranges. Categorical variables are presented as numbers and percentages. Patients were divided into two groups (TC and non-TC). To compare the two groups, Student t-test was used for continuous variables, and the chi-square test was used for categorical variables. Patients who underwent surgery or transcatheter arterial embolization (TAE) were selected and analyzed according to type of treatment center. Subgroup analysis of patients with ISS ≥ 16 among patients who underwent surgery and TAE was also performed.

To reduce the effects of confounding variables that influence outcome variables, when analyzing patients with severe trauma who underwent surgery or TAE, propensity score matching (PSM) was used to collect data in both groups. Trauma center patients were matched 1:1 with non-TC patients according to propensity score, using exact matching. To assess bias reduction in the PSM method, absolute standardized differences were calculated, with a value > 20% indicating a significant imbalance in the baseline covariate.

All statistical analyses were performed using R ver. 3.6.2 (R Foundation for Statistical Computing), and P-values were based on a two-sided significance level of 0.05.

**RESULTS**

**Characteristics of study subjects**

Of the 52,262 patients transported to EDs in Korea during the study period, 25,743 were considered suitable for the study and were included in the analysis. Patients who experienced cardiac arrest before ED visit (n = 6,018), visited the ED with nontraumatic causes and inadequate data for analysis (n = 10,235), and suffered an intentional injury (n = 10,266) were excluded. Among the included patients, 5,796 visited TCs and 19,947 visited non-TCs. Patient matching was achieved in 10.9% (2,800 of 25,743) of all patients, 24.2% (1,400 of 5,796) of those who visited TCs, and 7.0% (1,400 of 19,947) of those who visited non-TCs (Fig. 1).

**Main results**

We compared patient characteristics, including demographic variables, ISS, and injury mechanism, between the two groups. Compared with patients treated at non-TCs, patients treated at TCs were younger, predominantly male, had a disproportionately higher number of traffic-related injuries, and were more seriously injured, according to ISS. Notably, patients treated at non-TCs showed a shorter time from the 119 call to ED arrival by the emergency medical technician. Patients' medical outcomes were summarized by level of definitive trauma care. Compared to patients treated at non-TCs, patients treated at TCs were more likely to have a higher rate of surgery or TAE and higher admission rate through the ED. However, there was no significant difference in the survival rate of inpatients in the two groups (Table 1).

In previous results, patients treated at TCs had a higher hospitalization rate, resulting in a relatively lower interfacility transfer...
Survival benefit of transport to trauma centers

Table 1. Characteristics of patients with trauma in the ED (n=25,743)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TC (n = 5,796)</th>
<th>Non-TC (n = 19,947)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>48.6 ± 21.8</td>
<td>50.3 ± 23.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Injury Severity Score</td>
<td>11.5 ± 10.9</td>
<td>7.4 ± 8.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Time taken from 119 call to ED</td>
<td>37.7 ± 21.8</td>
<td>30.7 ± 21.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4,182 (72.2)</td>
<td>13,589 (68.1)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1,614 (27.8)</td>
<td>6,358 (31.9)</td>
<td></td>
</tr>
<tr>
<td>Insurance</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>National health insurance</td>
<td>3,119 (53.8)</td>
<td>12,623 (63.3)</td>
<td></td>
</tr>
<tr>
<td>Medical aid</td>
<td>234 (4.0)</td>
<td>1,362 (6.8)</td>
<td></td>
</tr>
<tr>
<td>Automobile insurance</td>
<td>2,443 (42.1)</td>
<td>5,962 (29.9)</td>
<td></td>
</tr>
<tr>
<td>Mechanism of injury</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Transportation incident</td>
<td>3,232 (55.8)</td>
<td>8,478 (42.5)</td>
<td></td>
</tr>
<tr>
<td>Fall from height</td>
<td>1,733 (29.9)</td>
<td>8,188 (41.0)</td>
<td></td>
</tr>
<tr>
<td>Nonaccidental blunt trauma</td>
<td>355 (6.1)</td>
<td>1,436 (7.2)</td>
<td></td>
</tr>
<tr>
<td>Stab/penetrating trauma</td>
<td>166 (2.9)</td>
<td>488 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Machine-related injury</td>
<td>165 (2.8)</td>
<td>279 (1.4)</td>
<td></td>
</tr>
<tr>
<td>Burn/chemical injury</td>
<td>49 (0.8)</td>
<td>348 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Strangulation/drowning</td>
<td>42 (0.7)</td>
<td>307 (1.5)</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>20 (0.3)</td>
<td>136 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>34 (0.6)</td>
<td>287 (1.4)</td>
<td></td>
</tr>
<tr>
<td>Survival outcome</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Survival</td>
<td>5,322 (91.8)</td>
<td>18,924 (94.9)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>474 (8.2)</td>
<td>1,023 (5.1)</td>
<td></td>
</tr>
<tr>
<td>Surgery or TAE performed</td>
<td>2,273 (39.2)</td>
<td>3,507 (17.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Outcome in ED</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Survival to discharge</td>
<td>1,710 (29.5)</td>
<td>9,045 (45.3)</td>
<td></td>
</tr>
<tr>
<td>Survival to transfer</td>
<td>274 (4.7)</td>
<td>3,190 (16.0)</td>
<td></td>
</tr>
<tr>
<td>Survival to admission</td>
<td>3,749 (64.7)</td>
<td>7,356 (36.9)</td>
<td></td>
</tr>
<tr>
<td>Died after CPR</td>
<td>55 (0.9)</td>
<td>288 (1.4)</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>8 (0.1)</td>
<td>68 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Intensive care unit admissiona)</td>
<td>2,592 (69.1)</td>
<td>3,330 (45.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Survival outcome after admissiona)</td>
<td></td>
<td></td>
<td>0.053</td>
</tr>
<tr>
<td>Survival</td>
<td>3,330 (88.8)</td>
<td>6,621 (90.0)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>419 (11.2)</td>
<td>735 (10.0)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number (%).

ED, emergency department; TC, trauma center; EMT, emergency medical technician; TAE, transcatheter arterial embolization; CPR, cardiopulmonary resuscitation.

a)3,749 TC and 7,356 non-TC.

rate than patients treated at non-TCs. Subsequently, transferred patients from TCs showed a lower intensive care unit (ICU) admission rate and a higher survival rate than patients from the non-TCs (Table 2). It was not known whether the transferred patients attended a TC or non-TC as the follow-up hospital.

We also compared non-TC and TC groups for patients who underwent surgery or TAE for their severe trauma treatment. Compared to patients treated at non-TCs, patients treated at TCs were notably younger and had higher ISS. Time taken for surgery or TAE at TCs was shorter (Table 3).

Table 2. Comparison of transferred patients’ outcomes in the ED (n=2,451)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>From TC (n = 177)</th>
<th>From non-TC (n = 2,274)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome in ED on second hospital</td>
<td></td>
<td></td>
<td>0.071</td>
</tr>
<tr>
<td>Survival to discharge</td>
<td>13 (7.3)</td>
<td>117 (5.1)</td>
<td></td>
</tr>
<tr>
<td>Survival to transfer</td>
<td>4 (2.3)</td>
<td>98 (4.3)</td>
<td></td>
</tr>
<tr>
<td>Survival to admission</td>
<td>160 (90.4)</td>
<td>2,010 (88.4)</td>
<td></td>
</tr>
<tr>
<td>Died after CPR</td>
<td>0 (0)</td>
<td>49 (2.2)</td>
<td></td>
</tr>
<tr>
<td>ICU admission on second hospitalb)</td>
<td>40 (25.0)</td>
<td>1,136 (56.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Survival outcome after admission on second hospitalb)</td>
<td></td>
<td></td>
<td>0.025</td>
</tr>
<tr>
<td>Survival</td>
<td>151 (94.4)</td>
<td>1,781 (88.6)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>9 (5.6)</td>
<td>229 (11.4)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number (%).

ED, emergency department; TC, trauma center; CPR, cardiopulmonary resuscitation; ICU, intensive care unit.

b)160 from TC and 2,010 from non-TC.

Table 3. Subgroup comparison of severe trauma patients who underwent surgery or TAE within 24 hours (n=3,384)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TC (n = 1,400)</th>
<th>Non-TC (n = 1,984)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>49.9 ± 18.7</td>
<td>52.9 ± 19.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Injury Severity Score ≥ 16</td>
<td>866 (61.9)</td>
<td>989 (49.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>0.474</td>
</tr>
<tr>
<td>Male</td>
<td>1,072 (76.8)</td>
<td>1,498 (75.5)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>328 (23.4)</td>
<td>486 (24.5)</td>
<td></td>
</tr>
<tr>
<td>Mechanism of injury</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Transportation incident</td>
<td>878 (62.7)</td>
<td>1,046 (52.7)</td>
<td></td>
</tr>
<tr>
<td>Fall from height</td>
<td>317 (22.6)</td>
<td>608 (30.6)</td>
<td></td>
</tr>
<tr>
<td>Nonaccidental blunt trauma</td>
<td>61 (4.4)</td>
<td>82 (4.1)</td>
<td></td>
</tr>
<tr>
<td>Stab/penetrating trauma</td>
<td>63 (4.5)</td>
<td>105 (5.5)</td>
<td></td>
</tr>
<tr>
<td>Machine-related injury</td>
<td>75 (5.4)</td>
<td>104 (5.2)</td>
<td></td>
</tr>
<tr>
<td>Burn/chemical injury</td>
<td>1 (0.1)</td>
<td>4 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Strangulation/drowning</td>
<td>0 (0)</td>
<td>3 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>0 (0)</td>
<td>6 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>5 (0.4)</td>
<td>22 (1.1)</td>
<td></td>
</tr>
<tr>
<td>Time taken from the ED to surgery or TAE (hr)</td>
<td>3.5 (2.0–7.8)</td>
<td>4.6 (2.7–9.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Survival outcome after admission</td>
<td></td>
<td></td>
<td>0.247</td>
</tr>
<tr>
<td>Survival</td>
<td>1,162 (83.0)</td>
<td>1,616 (81.5)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>238 (17.0)</td>
<td>368 (18.5)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation, number (%), or median (interquartile range).

TC, transcatheter arterial embolization; TC, trauma center; ED, emergency department.

This study used PSM to control for age, sex, and ISS in patients with severe trauma who underwent surgery or TAE. From each group, 1,400 patients were selected. The proportion of patients with ISS ≥ 16 was matched between the two groups. Lower in-hospital mortality was observed in the TC group than in the non-TC group (Table 4).
Table 4. Comparison of propensity score matched patients controlling for age, sex, and ISS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TC (n = 1,400)</th>
<th>Non-TC (n = 1,400)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>49.9 ± 18.7</td>
<td>50.1 ± 18.8</td>
<td>0.905</td>
</tr>
<tr>
<td>ISS ≥ 16</td>
<td>866 (61.9)</td>
<td>855 (61.1)</td>
<td>0.669</td>
</tr>
<tr>
<td>Sex</td>
<td>1,072 (76.6)</td>
<td>1,103 (78.8)</td>
<td>0.159</td>
</tr>
<tr>
<td>Survival outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival</td>
<td>1,162 (83.0)</td>
<td>1,101 (78.6)</td>
<td>0.003</td>
</tr>
<tr>
<td>Death</td>
<td>238 (17.0)</td>
<td>299 (21.4)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation or number (%). Patients are those who underwent surgery or transcatheter arterial embolization within 24 hours (n = 2,800).

ISS, Injury Severity Score; TC, trauma center.

DISCUSSION

In a past clinical analysis of patients with severe trauma, shortening the time from trauma to appropriate treatment was associated with reduced mortality [15]. Patients with severe trauma may not be able to quickly receive high-quality care when they are transported to non-TCs. Repeated interfacility transfer of patients and imaging may affect prognosis [16,17]. However, there is currently no clear distinction between non-TCs and TCs when transporting patients with severe trauma in Korea [10]. In this context, this study aimed to understand the effect of direct transport to the TC. Because the data were collected nationwide, this study should have a lower risk of sampling bias than previous studies.

In this study, patients transported directly to TCs were younger, and the proportion of male patients was higher than those transported to non-TCs. Trauma severity, identified as ISS, was higher and transportation to the emergency room took longer in TCs. Additionally, the proportion of traffic accidents tended to be higher in TCs. Regarding the characteristics of injuries related to traffic accidents, some studies have reported increased risk for young men and their greater inclination to engage in risky behaviors, such as speeding and consumption of alcohol or drugs, compared with women [18–21]. The overall mortality and neurological outcomes for men are not better, despite their younger age [22]. All these factors may affect treatment outcomes at TCs. Consistent with previous studies, there is a selection bias in which more severely impaired patients have priority transport to TCs. To the extent that selection bias is present, the TC population will be systematically different from the non-TC population [23]. This can complicate comparisons of survival rates between TCs and non-TCs and should be controlled in statistical analyses.

Patient treatment results were evaluated at the level of definitive treatment, such as surgery or arterial embolization [24,25]. Compared with patients treated in non-TCs, patients treated in TCs had more than twice the rate of surgical or arterial embolization, and the resulting hospitalization rate tended to be higher. Additionally, the ICU hospitalization rate for patients in non-TCs was higher than that for patients in TCs due to their high severity. However, there was no difference in survival rate between the two groups, possibly due to a combination of factors. Patients who were interfacility transferred from a non-TC had low survival-to-transfer rates, whereas all patients who were transferred from a TC had lower rates of ICU hospitalization and mortality. It can be interpreted that, among patients with severe trauma who needed immediate intensive care, fewer had to be transferred to a higher hospital level. In this respect, the effects of primary treatment in trauma centers can also be compared.

Because there was no difference in mortality between the two groups in the initial analysis, subgroup analysis was performed on patients who underwent surgery or TAE. A recent study by Ball et al. [26] suggested that the reduction in mortality in patients with vascular impairment was associated with an actual decrease in time spent within the ED and surgeon commitment to rapid transport to the operating room. In our study, although the time required for surgery or TAE in TCs was shorter, the difference in survival rates was not statistically significant.

We performed resampling using PSM for a controlled comparison of factors affecting the survival rate. After postmatching analysis, the difference of ISS score of TC patients and non-TC patients was not statistically significant. Through PSM, no statistical difference in the ratio of patients with severe trauma was observed. After adjusting for related factors, the survival rate of the TC patient group was significantly higher.

This study and its analysis process have several limitations. First, it was not known whether the transferred patients went to a TC or non-TC as the follow-up hospital. In this study, it was possible to compare the results of interfacility transferred patients according to the type of hospital of initial arrival. It is necessary to collect and supplement patient records from the follow-up hospital in future studies.

Second, we were unable to capture deaths that occurred shortly after discharge as a result of trauma injuries, even though Mullins et al. [27] demonstrated that many trauma deaths occur within 30 days of hospital discharge. Ideally, these deaths should have been included in the analysis [28].

Third, the data used in this study were from a single year and offer the advantage of representing Korea’s EMS at the national level. If data are accumulated over several years and follow-up studies are conducted, more meaningful and constructive results...
can be derived in the future.

Finally, even in the PSM analysis, we were unable to exclude numerous unknown confounding factors that may have affected the difference in TC status from outcomes after patient transportation. Other limitations are common to epidemiological studies, including ascertainment bias and lack of data integrity.

In this study, using data from the Korean EMS, we demonstrated that the direct transport of patients with severe trauma to TCs might lead to better survival benefits than transport to non-TCs.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

FUNDING

None.

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AUTHOR CONTRIBUTIONS

Conceptualization: DJL, SHK, HZC; Data curation: DJL, SHK, HZC; Formal analysis: DJL, JK, HZC; Investigation: DJL, HZC; Methodology: DJL, SHK, HZC; Project administration: DJL, MCK, HZC; Resources: DJL, HZC; Software: DJL, JK, HZC; Supervision: MCK, HZC; Validation: DJL, JK, HZC; Visualization: DJL, JK, HZC; Writing—original draft: DJL; Writing—review & editing: DJL, SHK, MCK, HZC. All authors read and approved the final manuscript.

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REFERENCES

Efficiency, limitations, and familiarization of a novel negative pressure aerosol box for intubation: a simulation-based randomized crossover study

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²SS-ENG Co., Ltd., Bucheon, Korea

Objective This study aimed to introduce a novel negative pressure aerosol box (Carrycure Isolator) and to test its efficiency and limitations, with the hope of suggesting improvements and further directions.

Methods A novel aerosol box (Carrycure Isolator) was invented. A single-center, randomized, crossover simulation study of 28 emergency medicine physicians was designed. Three trials of each participant using an intubation manikin were conducted, including intubation without the aerosol box (trial A), intubation with the aerosol box (trial B), and intubation with the aerosol box after familiarization (trial C). The primary endpoint was the time to intubation. The secondary endpoints were first-attempt success, number of attempts, percentage of glottic opening score, and Cormack-Lehane view. Collected data were statistically analyzed for their significance.

Results The median times to intubation of trials A, B, and C were 30.5 (interquartile range [IQR], 28.0–40.0 seconds), 59.0 (IQR, 50.0–75.5 seconds), and 34.0 seconds (IQR, 30.5–47.0 seconds), respectively. Post hoc analysis showed that the time to intubation in trial B was significantly longer than that in trial A (P < 0.05), while that the time to intubation in trial C was significantly shorter than that in trial B (P < 0.05). Results concerning secondary endpoints showed similar patterns. Participants reported performing intubation with Carrycure Isolator to be relatively difficult, necessitating significant arm movement and view restrictions while increasing their time to intubation.

Conclusion Physicians took a longer time to intubate a manikin using the Carrycure Isolator, a novel negative pressure aerosol box. However, the time was improved after a period of familiarization.

Keywords Patient isolators; Efficiency; Simulation training; Crossover studies; Intratracheal intubation
INTRODUCTION

The steep increase in confirmed COVID-19 cases with severe illness requiring hospitalization has led to a worldwide shortage of personal protective equipment and airborne infection isolation rooms [1]. To overcome the shortage of airborne infection isolation rooms, efforts have been made globally to develop isolation chambers or barriers known as “aerosol boxes” [2–10]. Despite their novelty, previous inventions have shown limitations. Some did not include a negative pressure device [3,5,6,10], others were simple barriers with open sides [10], and most did not have a slanted side, which can limit patient visualization [2,5,6,10]. Since severe COVID-19 cases often require aerosol-generating medical procedures (AGMPs), such as endotracheal intubation [11], having closed sides and maintaining negative pressure may mimic the effect of airborne infection isolation rooms and protect medical practitioners from pathogenic aerosols. Furthermore, a slanted viewing window enables the practitioner to approach the patient more closely and may provide a better view of the patient's airway while performing AGMPs. Because of the limitations of previously introduced aerosol boxes, our team recently developed a novel negative pressure aerosol box called the Carrycure Isolator (Severance Hospital) with closed sides, a negative pressure function, and a slanted viewing window. Our previous study of the Carrycure Isolator showed its efficacy in reducing contamination particles when performing intubation on a manikin [12]. However, its efficiency and usability have not yet been studied.

Despite the benefits of protecting medical practitioners from airborne illnesses, previous studies have shown that using an aerosol box limits the practitioner's ability to perform AGMPs and thereby increases intubation time [13–18]. As an increased intubation time may prolong hypoxia and increase patient risk, studies have been cautious about applying these aerosol boxes in actual medical practice [5,13]. Because the Carrycure Isolator is a more advanced form of an aerosol box, it is prone to the same challenges. Hence, this study aimed to test the efficiency of the Carrycure Isolator through a simulation-based randomized crossover study. We hypothesized that, although intubation time may initially increase when using the Carrycure Isolator for the first time, it can be improved with multiple practice sessions and proper guidance.

METHODS

Ethical statements

This study was approved by the Institutional Review Board of Severance Hospital, Yonsei University Health System (No. 1-2021-0087).

Trial design, participant selection, and randomization

According to Begley et al. [13], the average time to intubation with and without the latest form of an aerosol box was 42.5 and 52.5 seconds, respectively, with a mean ± standard deviation differential of 10.0 ± 7.5. Using G*Power ver. 3.1 (Heinrich Heine University Düsseldorf) with a 95% confidence interval and alpha value of 0.025, the minimum sample size was 10. After measuring the time to intubation by the instructor and assuming that the possibility that the mean of the difference would be reduced to 5, the minimum sample size was 26. Hence, we chose a sample size of 28 and designed a single-center, randomized, crossover simulation study of emergency medicine physicians at Severance Hospital. This study was conducted between February 13, 2022 and February 20, 2022, at Severance Hospital. Physicians with > 20 experiences of wearing personal protective equipment who were comfortable with endotracheal intubation with direct laryngoscopy were included, while those with physical disabilities or who were not willing to participate were excluded. A total of 30 emer-
Emergency medicine physicians (both specialists and residents) who volunteered to participate in this study were deemed eligible, but two were excluded due to personal schedules. The remaining 28 participants completed consent forms and were block-randomized using a random number generator and allocated into either group A or B. All participants were instructed to perform three intubations on a manikin to simulate AGMPs. To minimize learning bias, group A participants started with the control trial without the Carrycure Isolator, whereas group B participants started with the experimental trial with the Carrycure Isolator. Moreover, all participants were blinded to their group assignment. After both control and experimental trials, all participants went through a familiarization period for 10 minutes, where they were instructed to practice freely with the Carrycure Isolator and the manikin. No specific set of instructions was given to each participant, although the experimenter provided each participant with a tip during that period: “When preparing endotracheal intubation, placing the endotracheal tube on the right side and the laryngoscope on the left side will prevent crossing over of your hands and may reduce intubation time.” After familiarization, each participant performed the third trial. All participants were instructed to complete a survey questionnaire after completing the trials (Fig. 1).

Invention of Carrycure Isolator
Our team recently invented the Carrycure Isolator, which is made of a 1-cm-thick acrylic material with five closed sides. It has a 44.3 x 44.3-cm base and a maximum height of 44.3 cm at the patient entrance side so that it can fit into a computed tomography scanner. There are two connecting ports on both lateral sides for a negative pressure generating device. Four patient access orifices are also located on three sides, each with an outer iris diaphragm and an inner silicone slit. The outer iris diaphragm can be completely closed when not in use. Two of these orifices are on the practitioner’s side, whereas the other two are placed on the right and left sides of the chamber, respectively. Previously invented “box-shaped” aerosol boxes are mostly cubic, which can prevent the practitioner from approaching the patient inside the box. Endotracheal intubation using a direct laryngoscope often requires approaching the patient to visualize their airway and vocal cords. The Carrycure Isolator has a slanted viewing window that enables the practitioner to freely approach the patient and easily visualize their airway [12].

Materials
One Carrycure Isolator, bag valve mask (Ambu SPUR II Adult, Ambu A/S), airway manikin (Laerdal Airway Management Trainer, Laerdal Medical), 7-mm endotracheal tube with a stylet, direct laryngoscope with Mac 4 blade, and 10-cc syringe were used for this study. The manikin was placed on a flat surface, and its height was adjusted by each participant to their most comfortable position to simulate the height-adjustable nature of the stretcher. Each participant was provided with new personal protective equipment (surgical gowns, nitrile gloves, masks, surgical caps, and protective goggles) for each trial (Fig. 2).

Endpoints and data collection
The primary endpoint of this study was time to intubation, which was defined as the time from the end of preoxygenation to the first ventilation after successful endotracheal intubation, as visualized by the inflation of both lungs on the manikin. Since Begley et al. [13] in their previous study used 180 seconds as a cutoff value for successful intubation in an aerosol box, when the participant required > 180 seconds to intubate, the trial was considered a failure, and they were instructed to restart the procedure. Then, only the time to intubation during a successful trial was collected. The secondary endpoints were first-attempt success, number of attempts, percentage of glottic opening (POGO) score,
and Cormack-Lehane view. A single attempt was defined as the single entrance of the direct laryngoscope into the oral cavity of the manikin. The time to intubation, first-attempt success, and number of attempts were measured and observed by the experimenter and recorded on the datasheet during the trial. The POGO score, Cormack-Lehane view, relative difficulty, relative arm restriction, relative viewing restriction, and subjective increase in intubation time were reported by each participant after the trial during a survey questionnaire, together with personal information such as age, sex, and length of experience in the emergency department. The POGO score was established on a 4-point scale as follows: 1 point, 0% to 25%; 2 points, 25% to 50%; 3 points, 50% to 75%; and 4 points, 75% to 100%. Relative measures were reported on a 5-point scale where 1 point represents “not at all” and 5 points represent “significantly increased.”

Statistical analysis
As our study considered three repeated trials for each participant, we performed a parametric analysis, assuming that the data from each trial were correlated. Friedman test and the Wilcoxon signed-rank test were used for continuous and ordinal dependent variables, respectively, and the Cochran’s Q test and McNemar’s test were used for binary dependent variables. As a continuous variable, time to intubation was presented with median and inter-quartile range (IQR) values. All tests were two-sided, with a cut-off P-value of <0.05. A post hoc analysis was performed using the Bonferroni adjustment. Because three trials were performed, P < 0.017 (0.05/3) was considered to be statistically significant. All statistical analyses were performed using SAS ver. 9.4 (SAS Institute Inc).

RESULTS
A total of 84 intubations were performed by 28 participants, all of whom were emergency medicine physicians. Although most participants (85.7%) were residents, all reported that they were confident in intubating using a direct laryngoscope. The mean age of the participants was 29.8 years, and their mean length of experience in the emergency department was 3.2 years. Other demographic information is presented in Table 1.

As a primary endpoint, the median times to intubation during the trials without the Carrycure Isolator (trial A), with the Carrycure Isolator (trial B), and with the Carrycure Isolator after familiarization (trial C) were 30.5 seconds (IQR, 28.0–40.0 seconds), 59.0 seconds (IQR, 50.0–75.5 seconds), and 34.0 seconds (IQR, 30.5–47.0 seconds), respectively (Fig. 3). The overall statistical analysis revealed that all three trials had significant differences in the time to intubation (P < 0.001). Post hoc analysis showed that the time to intubation in trial B was significantly longer than that in trial A (P < 0.017), while the time to intubation in trial C was
significantly shorter than that in trial B (P < 0.017). However, when comparing trials A and C, there was still a significant time increase, even after practice (P = 0.008) (Table 2).

As secondary endpoints, none of the participants failed to intubate during their first attempt in trial A, while six participants required > 1 attempt in trial B and one participant required > 1 attempt in trial C. There was a significant difference in first-pass success (P < 0.050) and the number of attempts (P < 0.050) when comparing all three trials. However, a post hoc analysis of first-pass success and number of attempts did not highlight a significant increase when comparing trials A and B (P = 0.031 and P = 0.031, respectively), A and C (P = 0.125 and P = 0.094, respectively), or B and C (P > 0.999 and P > 0.999, respectively). The self-reported POGO score and Cormack-Lehane view also were significantly different overall among the trials (P < 0.017). A post hoc analysis showed that the POGO scores of trials A and C were significantly higher than that of trial B (P < 0.017); in contrast, the POGO score difference between trials A and C was not significant (P = 0.022), indicating that familiarization improved the view of the vocal cords. A post hoc analysis of the Cormack-Lehane view

Table 1. Clinical and demographic information of the participants (n=28)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specialty (emergency medicine)</td>
<td>28 (100)</td>
</tr>
<tr>
<td>Training</td>
<td></td>
</tr>
<tr>
<td>Resident</td>
<td>23 (82.1)</td>
</tr>
<tr>
<td>Board-certified emergency medicine physician</td>
<td>5 (17.9)</td>
</tr>
<tr>
<td>Reported self-efficacy</td>
<td></td>
</tr>
<tr>
<td>Confident in intubating using a direct laryngoscope</td>
<td>28 (100)</td>
</tr>
<tr>
<td>Not confident in intubating using a direct laryngoscope</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17 (60.7)</td>
</tr>
<tr>
<td>Female</td>
<td>11 (39.3)</td>
</tr>
<tr>
<td>Clinical experience in the emergency department (yr)</td>
<td>3.18 (1–10)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>29.8 (26–36)</td>
</tr>
</tbody>
</table>

Values are presented as number (%) or average (range).

Table 2. Primary and secondary outcomes of the three trials (n=28)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Trial A</th>
<th>Trial B</th>
<th>Trial C</th>
<th>Overall (P-value)</th>
<th>Post hoc analysis (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (sec)</td>
<td>30.5 (28.0–40.0)</td>
<td>59.0 (50.0–75.5)</td>
<td>34.0 (30.5–47.0)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>First-pass success</td>
<td>28 (100)</td>
<td>22 (78.6)</td>
<td>27 (96.4)</td>
<td>0.012</td>
<td>0.031</td>
</tr>
<tr>
<td>No. of attempts</td>
<td></td>
<td></td>
<td></td>
<td>0.012</td>
<td>0.031</td>
</tr>
<tr>
<td>1</td>
<td>28 (100)</td>
<td>22 (78.6)</td>
<td>27 (96.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0 (0)</td>
<td>4 (14.3)</td>
<td>1 (3.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0 (0)</td>
<td>2 (7.1)</td>
<td>0 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>POGO score (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>0–25</td>
<td>0 (0)</td>
<td>2 (7.1)</td>
<td>0 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25–50</td>
<td>1 (3.6)</td>
<td>10 (35.7)</td>
<td>2 (7.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–75</td>
<td>6 (21.4)</td>
<td>11 (39.3)</td>
<td>12 (42.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75–100</td>
<td>21 (75.0)</td>
<td>5 (17.9)</td>
<td>14 (50.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cormack-Lehane view</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Grade I</td>
<td>24 (85.7)</td>
<td>5 (17.9)</td>
<td>13 (46.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade II</td>
<td>4 (14.3)</td>
<td>17 (60.7)</td>
<td>13 (46.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade III</td>
<td>0 (0)</td>
<td>6 (21.4)</td>
<td>2 (7.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade IV</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range) or number (%).
POGO, percentage of glottic opening.
Performed intubation †without Carrycure Isolator, ‡with Carrycure Isolator, and ‡with Carrycure Isolator after familiarization.

Fig. 3. Box-and-whisker plot of the three trials. Interquartile range and median are noted on the diagram. †P < 0.017.
Table 3. Adjunctive survey questionnaire after experience with the Carrycure Isolator

<table>
<thead>
<tr>
<th>Reported posttrial questionnaire</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intubation with the Carrycure Isolator was more difficult</td>
<td>2.64^4</td>
</tr>
<tr>
<td>1</td>
<td>4 (14.3)</td>
</tr>
<tr>
<td>2</td>
<td>11 (39.3)</td>
</tr>
<tr>
<td>3</td>
<td>4 (14.3)</td>
</tr>
<tr>
<td>4</td>
<td>9 (32.1)</td>
</tr>
<tr>
<td>5</td>
<td>0 (0)</td>
</tr>
<tr>
<td>The Carrycure Isolator limited arm movement</td>
<td>4.00^4</td>
</tr>
<tr>
<td>1</td>
<td>0 (0)</td>
</tr>
<tr>
<td>2</td>
<td>3 (10.7)</td>
</tr>
<tr>
<td>3</td>
<td>2 (7.1)</td>
</tr>
<tr>
<td>4</td>
<td>15 (53.6)</td>
</tr>
<tr>
<td>5</td>
<td>8 (28.6)</td>
</tr>
<tr>
<td>The Carrycure Isolator limited the view</td>
<td>3.68</td>
</tr>
<tr>
<td>1</td>
<td>0 (0)</td>
</tr>
<tr>
<td>2</td>
<td>5 (17.9)</td>
</tr>
<tr>
<td>3</td>
<td>5 (17.9)</td>
</tr>
<tr>
<td>4</td>
<td>12 (42.9)</td>
</tr>
<tr>
<td>5</td>
<td>6 (21.4)</td>
</tr>
<tr>
<td>It felt like using the Carrycure Isolator increased the time to intubation</td>
<td>3.89^4</td>
</tr>
<tr>
<td>1</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>2</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>3</td>
<td>4 (14.3)</td>
</tr>
<tr>
<td>4</td>
<td>16 (57.1)</td>
</tr>
<tr>
<td>5</td>
<td>6 (21.4)</td>
</tr>
</tbody>
</table>

Each question was rated on a scale of 1 to 5 points (1, not at all; 2, slightly; 3, moderately; 4, significantly; 5, absolutely).

^4Average points.

confirmed a similar pattern when comparing trials A and C with trial B, although the reported data of trial C suggested a significant decrease in the Cormack-Lehane view compared to those of trial A (Table 2).

The results from the adjunctive survey questionnaire about participants’ experience with the Carrycure Isolator are presented in Table 3. Participants felt that performing intubation using the Carrycure Isolator was relatively difficult (mean, 2.64 points), led to significant arm movement restrictions (mean, 4 points), required significant view restrictions (mean, 3.68 points), and significantly increased their time to intubation (mean, 3.89 points).

**DISCUSSION**

This study aimed to introduce a novel aerosol box, the Carrycure Isolator, and to test its efficiency. Price et al. [16], in their review article, categorized efficacy, usability, and efficiency as three important aspects to investigate when testing an aerosol box. Efficacy represents the ability to contain aerosol inside the box, usability refers to the user experience, and efficiency is indicated by the time to intubation [16]. Previous studies on negative pressure aerosol boxes or vacuum-assisted aerosol boxes have proven their efficacy by showing reduced particles during intubation of a manikin [19,20]. Our previous study with the Carrycure Isolator also proved its efficacy by showing a reduction of particles outside the Carrycure Isolator during simulated AGMPs performed on a manikin [12]. To test the Carrycure Isolator’s efficiency, we measured the time to intubation along with the other secondary outcomes mentioned above.

Our results showed that using the Carrycure Isolator significantly increased the time to intubation. This result was consistent with those of previous aerosol box studies conducted on a manikin [13,14]. In their systemic review and meta-analysis, Lim et al. [21] also reported that using an aerosol box in general significantly increased the time to intubation, but they mentioned that more experienced medical practitioners achieved a shorter time to intubation. However, previous studies have not focused on the effects of practice when testing aerosol boxes. Our results demonstrated that, after sufficient practice and guidance, the time to intubation was significantly decreased (59.0 seconds vs. 34.0 seconds, \( P < 0.017 \)), although it remained longer than that of the control group (30.5 seconds vs. 34.0 seconds, \( P = 0.008 \)). Owing to the slanted nature of the viewing window of the Carrycure Isolator, participants often experienced a collision of the connector side of the endotracheal tube with the viewing window, thereby interrupting tube advancement. In addition, because of the inevitable cramped nature of the aerosol box, participants had difficulty grasping materials on the opposite side of their hands. Some authors have presented a larger box or tent-like devices that may solve these difficulties [4,9,14]. However, the Carrycure Isolator was purposefully designed with specific dimensions so that the practitioner can approach the patient while performing intubation, and it can be used inside the computed tomography scanner while maintaining negative pressure. Most of the participants felt that the tip provided by the instructor during the familiarization period was useful and reported that, with sufficient practice, these inconveniences could be overcome. In addition, some participants felt that bending the connector portion of the endotracheal tube facilitated tube insertion and prevented a collision with the viewing window. Although this bending of the tube may benefit insertion attempts, it may also interrupt the removal of the stylet from the tube. Thus, further studies on more flexible and softer stylet materials should be conducted to improve both tube insertion and stylet removal.

First-pass success and fewer total attempts may be critical in patients requiring endotracheal intubation. Our data revealed significant differences among the three trials. When participants
used the Carrycure Isolator for the first time, the first-time success rate was significantly decreased. However, even after sufficient practice, there was no significant difference. Meanwhile, although no significant increase in first-pass success was found when comparing trials B and C, we believe this result is due to the small sample size since all six participants who initially failed to achieve first-pass success succeeded after the familiarization period.

Although self-reported, the Cormack-Lehane view showed a similar pattern to that of time to intubation, where significant improvement was reported after familiarization. In addition to the effect of practice, we believe that the slanted viewing window also aids in vocal cord visualization. Further studies should be designed to test the effect of the slanted viewing window of the Carrycure Isolator by directly comparing it to a cubic aerosol box.

Participants’ completion of survey questions after the trials revealed negative reports on difficulty, movement restrictions, view restrictions, and perceived increased time to intubation. We believe that these results are due to the compact nature of the aerosol box. Further design modifications using malleable materials or variable sizes should be considered to overcome these difficulties.

Despite the novel nature and benefits of the Carrycure Isolator, our study has the following limitations. First, this was only a simulation-based manikin study. Since every individual patient has different airway structures, and patients often present with difficult airways, the results may differ when human subjects are used. Further studies on the efficiency of the Carrycure Isolator in patients or manikins with difficult airways should be considered. Second, because most of the participants were residents, a lack of experience may have caused an increase in intubation time. Although all participants reported that they were comfortable with endotracheal intubation using a direct laryngoscope, their mean age was 29.8 years and their mean experience in the emergency room was only 3.2 years. As endotracheal intubation is a critical procedure that often requires years of experience, our study may not reflect the entire physician population. Third, this study was performed using a direct laryngoscope. As videoscopy is becoming increasingly available worldwide, further studies with a videoscope should be conducted to improve the view of the vocal cords, although the size of this device may not be completely suitable for the Carrycure Isolator. Finally, since we conducted trial C right after the familiarization period, the long-term effects of practice should be examined in a future study.

Using an aerosol box challenges medical practitioners during AGMPs and increases their time to intubation. The same was true for our novel aerosol box, the Carrycure Isolator. However, our study showed that, after sufficient practice and proper guidance, the time to intubation is improvable on a manikin. Therefore, future attempts should be made to educate practitioners on the use of aerosol boxes, including how to apply them safely in actual medical practice.

**CONFLICT OF INTEREST**

Ideas in this study are included in a pending patent in Korea, and Severance Hospital (Seoul, Korea) signed a technology transfer contract with SJ Science (Seoul, Korea). If this technology is commercialized, the first and corresponding authors/inventors of this product might receive remuneration. However, the authors received no personal benefits from SJ Science.

**FUNDING**

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**AUTHOR CONTRIBUTIONS**

Conceptualization: JYH, KSS; Data curation: YP, KSS; Formal analysis: YP, JHK; Funding acquisition: JYH, KSS; Visualization: JYH, YP; Writing–original draft: JYH, YP; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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**REFERENCES**


A study on computed tomography cardiothoracic ratio in predicting left ventricular systolic dysfunction

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Objective A cardiothoracic ratio ≥ 0.50 is widely used as an indicator of cardiomegaly, but associations between the cardiothoracic ratio and left ventricular systolic dysfunction (LVSD) have not been investigated previously. We conducted this study to investigate the relationship between cardiothoracic ratio measured using computed tomography (CT) and left ventricular ejection fraction (LVEF), and to determine the optimal cardiothoracic ratio for predicting left ventricular systolic dysfunction (LVSD).

Methods A retrospective cross-sectional study was performed using data from patients who underwent both chest CT and echocardiography at the emergency department from January 1 to December 31, 2021. The patients were classified as normal, or having mild, moderate, and severe LVSD based on their LVEF, and the cardiothoracic ratios of each group were compared. The receiver operating characteristic (ROC) curve analyses were used to identify the optimal cardiothoracic ratio for prediction of mild, moderate, and severe LVSD.

Results The final study population included 444 patients. The median CT-measured cardiothoracic ratio was 0.54 for patients with normal LVEF, and 0.60 for patients with LVSD (P < 0.001). The optimal CT-measured cardiothoracic ratios for predicting mild, moderate, and severe LVSD were 0.56, 0.59, and 0.60, and their areas under the ROC curve were 0.653, 0.690, and 0.680, and negative predictive values were 90%, 94%, and 98%, respectively.

Conclusion The best cutoff value for a CT-measured cardiothoracic ratio suggestive of LVSD was 0.56, which is very different from the 0.50 value typically considered an abnormal cardiothoracic ratio. The CT-measured cardiothoracic ratio ≥ 0.56 can be used as a rough indicator of mild LVSD, and a ratio < 0.60 can exclude severe LVSD with a high degree of confidence.

Keywords Cardiothoracic ratio; Stroke volume; Cardiomegaly; Computed tomography; Thoracic radiography

What is already known
A cardiothoracic ratio >0.50 is a well-known indicator of cardiomegaly on chest radiographs.

What is new in the current study
The best cutoff values for computed tomography-measured cardiothoracic ratios suggestive of mild, moderate, and severe left ventricular systolic dysfunction (LVSD) were 0.56, 0.59, and 0.60, respectively. Cardiothoracic ratios have high negative predictive value for LVSD, and a cardiothoracic ratio <0.60 can exclude severe LVSD with a high degree of confidence.
INTRODUCTION

First described in 1919, the cardiothoracic ratio is the most widely used classic indicator of cardiomegaly on chest radiographs [1]. The cardiothoracic ratio is the ratio of the maximum horizontal heart diameter to the maximum horizontal chest diameter measured in the posteroanterior (PA) thoracic radiograph and is calculated using up to two decimal places. A cardiothoracic ratio of 0.42 to 0.50 in PA thoracic radiographs is considered normal. Previous studies have reported that an elevated cardiothoracic ratio (>0.50) is significant for prognostic assessment in healthy adults [2], the elderly [3], and patients with various congenital [4] and acquired heart diseases [5–10]. In addition, Shah et al. [11] reported that a cardiothoracic ratio greater than 0.50 was a good predictor of decreased left ventricular systolic function. In addition, in a group of hemodialysis patients, cardiothoracic ratios greater than 0.55 were found to be the most important independent prognostic factor associated with all-cause mortality within 2 years [12], and in patients undergoing valve replacement, a cardiothoracic ratio greater than 0.60 is known to be an independent prognostic factor associated with death in the 1st year after valve replacement [13].

The cardiothoracic ratio should not be measured on anteroposterior (AP) chest radiographs because the heart shadow is artificially enlarged due to the divergence of the X-ray beam. However, chest radiography is often performed using the AP view rather than the PA view for patients with impaired mobility, making it impossible to measure the cardiothoracic ratio. Kim et al. [14] reported that the cardiothoracic ratio can easily be obtained by measuring the maximum heart width divided by the maximum chest width in single computed tomography (CT) images and can predict the presence of a cardiomegaly if the cardiothoracic ratio exceeds 0.50. CT is performed very frequently in the emergency department (ED), and when CT is performed, the cardiothoracic ratio can be measured by CT instead of chest radiography. We conducted this study to investigate the associations between the cardiothoracic ratio measured by chest CT and left ventricular systolic function measured by echocardiography, and to determine the best cardiothoracic ratio to predict left ventricular systolic dysfunction (LVSD).

METHODS

Ethical statements

This study was implemented after approval by the Institutional Review Board of Kangbuk Samsung Hospital (No. 2022-06-058). The Institutional Review Board exempted written informed consent due to the retrospective nature of the study. Personal information, such as patient name, date of birth, and social identification number, was deleted after assigning research subject numbers to ensure anonymity. This study was conducted in compliance with the World Medical Association Declaration of Helsinki [15].

Study design and subjects

A retrospective cross-sectional study of adult patients over the age of 18 years was conducted. The study included patients who underwent both (contrast or noncontrast enhancement) chest CT and echocardiography in the ED. The exclusion criteria were (1) an interval of more than 24 hours between CT and echocardiography imaging (given left ventricular ejection fraction [LVEF] may change over time if there is a change in systemic vascular resistance or effective circulating volume, or if the heart becomes hyperdynamic); (2) no LVEF report on echocardiography; and (3) anatomical abnormalities rendering heart or chest transverse diameter measurement on CT images impossible (Fig. 1).

The sample size for multivariate logistic regression was calculated using the following formula based on Peduzzi’s research: \[ N = 10 \times k/p, \] where \( k \) is the number of independent variables and...
p is the smallest of the proportions of negative or positive cases in the population [16]. When calculated using the above method, and assuming five independent variables to be included in the analyses, and that the probability of a case of reduced left ventricular systolic function (LVEF < 50%) based on the results of echocardiography herein is 18%, the minimum sample size required was determined to be 278 cases. To satisfy the minimum sample size, the retrospective study period was set to the past 1 year.

Outcome measures
During the study, CT scans were performed using a Brilliance iCT-SP 128 CT scanner (Philips Medical Systems) in accordance with the protocol of the radiology department. The default values for the recombinant parameters used were a 2-mm slice thickness and 2-mm slice spacing. The measurements were performed using the length measurement tool built into the INFINITT PACS viewer (INFINITT Healthcare) program in a 27-inch FHD (1,920 x 1,080) resolution monitor environment. To select an axial image with maximal cardiac width, the axial images were continuously moved on the mediastinum window setting, cross-referencing the mid-sagittal image on a 1 x 2-split screen. The maximum heart width was measured in the selected axial image and the maximum chest width was measured in the same image. If there was a shadow presumed to be pericardial effusion or pericardial fat, this shadow was included in the measurement of the maximal cardiac width. The maximum chest width was measured between the inner edges of the ribs. In this way, the CT cardiothoracic ratio was calculated as the value obtained by dividing the maximum heart width by the chest width in the same image (Fig. 2). The cardiothoracic ratio was measured by three emergency physicians and the interobserver agreement between the observers was assessed using the intraclass correlation coefficient (ICC). The ICC and the 95% confidence interval (CI) were calculated by the two-two-way random-effects model in condition of absolute agreement (k = 3).

LVEF was retrieved from the final echocardiography report. During the study period, echocardiography was performed by certified sonographers and the final report was confirmed by the attending cardiologist. Either the Teichholz or modified Simpson method was used to measure the ejection fraction. The Teichholz method was adopted for patients who did not have regional left ventricular wall motion abnormalities (RWMA) and the modified Simpson method was adopted for patients with RWMA. Normal left ventricular systolic function was defined as an LVEF of 50% or more, mild LVSD was defined as an LVEF of 40% to 49%, moderate LVSD was defined as an LVEF of 30% to 39%, and severe LVSD was defined as an LVEF less than 30%.

Statistical analyses
All statistical analyses were performed using Stata ver. 15.1 (Stata Corp). Continuous variables were analyzed using a nonparametric method (Mann-Whitney U-test) because they did not follow a normal distribution, and representative values were presented as medians and interquartile ranges. Nominal variables were analyzed using a chi-square test and presented as frequencies and percentages. A P-value of less than 0.05 was considered to statistically significant. A logistic regression analysis was performed to analyze whether the classic cardiothoracic ratio of 0.5 or higher is correlated with LVSD. Comparison of the cardiothoracic ratio

Fig. 2. Measuring the cardiothoracic ratio on computed tomography (CT). The cardiothoracic ratio was calculated by measuring the diameter of the heart (solid line) and the diameter of the chest (dotted line) on the axial CT image where the transverse diameter of the heart appeared widest. The measurements were obtained on the same basis for both (A) noncontrast CT and (B) contrast-enhanced CT images.
according to the degree of LVSD (normal, mild, moderate, and severe LVSD) was performed using a one-way analysis of variance. Using receiver operating characteristic (ROC) curve analyses, the optimal cutoff values of the cardiothoracic ratio to predict mild, moderate, and severe LVSD were calculated, and the sensitivity and specificity of each cutoff value were calculated. We interpreted area under the ROC curve (AUC) values between 0.9 and 1.0 as being excellent, 0.8 to 0.9 as good, 0.7 to 0.8 as fair, 0.6 to 0.7 as poor, and 0.5 to 0.6 as failures.

RESULTS

The study period was 1 year from January 1, 2021 to December 31, 2021. During the study period, 1,119 adult patients underwent both (noncontrast or contrast-enhanced) chest CT and echocardiography in our ED. Of these 1,119 patients, 672 were excluded because they underwent echocardiography 24 hours after CT, and another three patients were excluded because their echocardiography report did not describe the LVEF. Finally, 444 patients were selected as study subjects (Fig. 1). The reasons for echocardiography were to rule out heart failure (39.2%), rule out ischemic heart disease (28.4%), rule out cor pulmonale (6.3%), rule out aortic disease (6.1%), fever workup (5.6%), rule out pericardial disease (4.1%), rule out valvular heart disease (3.8%), rule out cardiomyopathy (3.4%), chest trauma (1.8%), postcardiac-arrest workup (0.9%), and preoperative check (0.5%). There were no patients with anatomical deformities severe enough to prevent measurement of the cardiothoracic ratio.

The degree of consistency between the three measurers of the cardiothoracic ratio measurement was excellent. The ICC for the maximum heart width measurement was 0.959 (95% CI, 0.909–0.981; P < 0.001), and the ICC for the maximum chest width measurement was 0.937 (95% CI, 0.885–0.967; P < 0.001).

The general characteristics of the study subjects are presented in Table 1. The mean age of patients who underwent both chest CT and echocardiography within 24 hours in the ED was 78 years. Among all study subjects, 18.7% had LVSD. The median cardiothoracic ratio of patients with LVSD was 0.60, which was significantly different from the median cardiothoracic ratio of 0.54 in patients with normal left ventricular function (Table 1).

The median cardiothoracic ratio according to the degree of LVSD is presented in Table 2. Of the 444 total subjects, 81.3% had normal left ventricular systolic function, and their median cardiothoracic ratio was 0.54. The median cardiothoracic ratios of the mild, moderate, and severe LVSD groups were 0.57, 0.60, and 0.61, respectively. The cardiothoracic ratios differed significantly be-

### Table 1. General characteristics of the study patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n= 444)</th>
<th>LVEF ≥ 50% (n= 361)</th>
<th>LVEF &lt;50% (n= 83)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>78 (66–84)</td>
<td>78 (65–84)</td>
<td>80 (72–85)</td>
<td>0.031</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>224 (50.4)</td>
<td>195 (54.0)</td>
<td>29 (34.9)</td>
<td>0.002</td>
</tr>
<tr>
<td>Male</td>
<td>220 (49.6)</td>
<td>166 (46.0)</td>
<td>54 (65.1)</td>
<td></td>
</tr>
<tr>
<td>Initial vital signs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>87 (76–105)</td>
<td>84 (75–102)</td>
<td>99 (85–113)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Body temperature (°C)</td>
<td>36.8 (36.3–37.3)</td>
<td>36.8 (36.3–37.4)</td>
<td>36.6 (36–36.9)</td>
<td>0.003</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>137 (120–164)</td>
<td>138 (120–165)</td>
<td>135 (118–161)</td>
<td>0.562</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>77 (65–88)</td>
<td>77 (64–88)</td>
<td>81 (69–93)</td>
<td>0.047</td>
</tr>
<tr>
<td>Oxygen saturation (%)</td>
<td>97 (95–99)</td>
<td>97 (95–99)</td>
<td>97 (95–98)</td>
<td>0.912</td>
</tr>
<tr>
<td>Time interval between CT and echocardiography (hr)</td>
<td>6 (2–15)</td>
<td>6 (1–15)</td>
<td>7 (2–17)</td>
<td>0.341</td>
</tr>
<tr>
<td>Laboratory test result</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>proBNP (pg/mL)</td>
<td>1,568 (288–4,897)</td>
<td>1,063 (182–3,523)</td>
<td>5,710 (2,841–15,517)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Troponin I (ng/mL)</td>
<td>19.02 (10.00–100.28)</td>
<td>11.97 (10.00–76.47)</td>
<td>67.80 (21.92–250.50)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CK-MB (ng/mL)</td>
<td>1.71 (0.92–3.22)</td>
<td>1.52 (0.85–2.80)</td>
<td>2.70 (1.67–4.99)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.94 (0.73–1.46)</td>
<td>0.92 (0.71–1.30)</td>
<td>1.06 (0.83–2.03)</td>
<td>0.003</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>11.5 (9.8–13.3)</td>
<td>11.5 (9.8–13.1)</td>
<td>11.7 (9.8–13.7)</td>
<td>0.414</td>
</tr>
<tr>
<td>Echocardiographic finding (LVEF, %)</td>
<td>63 (53–69)</td>
<td>65.2 (59–70)</td>
<td>35 (30–43)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CT measurement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac diameter (mm)</td>
<td>132.8 (121.8–144.7)</td>
<td>130.7 (120.9–142.2)</td>
<td>141.9 (132.0–154.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Thoracic diameter (mm)</td>
<td>241.0 (226.5–256.6)</td>
<td>240.6 (226.9–256.3)</td>
<td>241.9 (224.5–260.0)</td>
<td>0.856</td>
</tr>
<tr>
<td>Cardiothoracic ratio</td>
<td>0.55 (0.51–0.61)</td>
<td>0.54 (0.5–0.6)</td>
<td>0.60 (0.55–0.64)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Values are presented as the median (interquartile range) or number (%).
LVEF, left ventricular ejection fraction; CT, computed tomography; BNP, brain natriuretic peptide; CK-MB, creatine kinase-MB.
The results of this study showed that the median cardiothoracic ratio in the normal left ventricular systolic function group was 0.54 (interquartile range, 0.50–0.60), and that the traditional abnormal cardiothoracic ratio standard of 0.50 cannot be utilized to

Table 2. Cardiorespiratory ratios measured by computed tomography according to LVEF (n=444)

<table>
<thead>
<tr>
<th>Group</th>
<th>Frequency</th>
<th>Cardiorespiratory ratio</th>
<th>P-value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>vs. normal</td>
<td>vs. mild dysfunction</td>
</tr>
<tr>
<td>Normal</td>
<td>361 (81.3)</td>
<td>0.54 (0.50–0.60)</td>
<td>-</td>
</tr>
<tr>
<td>Mild dysfunction</td>
<td>32 (7.2)</td>
<td>0.57 (0.52–0.63)</td>
<td>0.055</td>
</tr>
<tr>
<td>Moderate dysfunction</td>
<td>31 (7.0)</td>
<td>0.60 (0.55–0.64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe dysfunction</td>
<td>20 (4.5)</td>
<td>0.61 (0.57–0.65)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are presented as number (%) or median (interquartile range). The patients were classified based on their LVEF: normal, ≥50%; mild dysfunction, 40%–49%; moderate dysfunction, 30%–39%; severe dysfunction, <30%.

LVEF, left ventricular ejection fraction.

<sup>a</sup>Tukey test was used for multiple comparisons.

Table 3. Predictive value of a cardiothoracic ratio greater than the 0.50 standard to identify a left ventricular ejection fraction less than 50%

<table>
<thead>
<tr>
<th>Cardiorespiratory ratio</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥0.50</td>
<td>87</td>
<td>23</td>
<td>35</td>
<td>21</td>
<td>88</td>
<td>0.054</td>
</tr>
</tbody>
</table>

PPV, positive predictive value; NPV, negative predictive value; OR, odds ratio.

Table 4. Optimal cardiothoracic ratio measured by computed tomography to predict LVSD

<table>
<thead>
<tr>
<th>LVSD</th>
<th>Optimal cardiothoracic ratio</th>
<th>AUC</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>OR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>≥0.56</td>
<td>0.653</td>
<td>72</td>
<td>55</td>
<td>59</td>
<td>27</td>
<td>90</td>
<td>3.24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Moderate to severe</td>
<td>≥0.59</td>
<td>0.690</td>
<td>66</td>
<td>69</td>
<td>69</td>
<td>21</td>
<td>94</td>
<td>4.12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe</td>
<td>≥0.60</td>
<td>0.680</td>
<td>70</td>
<td>72</td>
<td>71</td>
<td>10</td>
<td>98</td>
<td>5.84</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

LVSD were classified based on left ventricular ejection fraction: all, <50%; moderate to severe, <40%; severe, <30%.

LVSD, left ventricular systolic dysfunction; AUC, area under receiver operating characteristic curve; PPV, positive predictive value; NPV, negative predictive value; OR, odds ratio.

The optimal cardiothoracic ratios for prediction of mild, moderate, and severe LVSD were 0.56, 0.59, and 0.60, respectively. The AUC of the 0.56 cardiothoracic ratio cutoff value for mild LVSD was 0.653, and was 0.690 for the 0.59 cutoff for moderate LVSD, and 0.680 for the 0.60 cutoff for severe LVSD. There was no cardiothoracic ratio criterion with an AUC of 0.700 or more (Table 4).

When applying the traditional abnormal cardiothoracic ratio threshold of 0.50, the odds ratio for LVSD (LVEF <50%) was only 1.95 and there was no significant difference (Table 3).

The positive predictive value (PPV) of the cardiothoracic ratio to predict LVSD was less than 30%, and the negative predictive value (NPV) was very high (≥ 90%) (Table 4). Only 23 patients (5.18%) had LVSD despite having cardiothoracic ratios of 0.56 or less, while 18 patients (4.1%) had moderate or severe LVSD despite having cardiothoracic ratios of 0.59 or less, and nine patients (2.0%) had severe LVSD despite cardiothoracic ratios of 0.60 or less. There were four atypical patients who had a LVEF of <40% even though they had a cardiothoracic ratio of <0.5 (Fig. 3).

![Linear prediction](80 60 40 20 0.3 0.4 0.5 0.6 0.7 0.8 Cardiothoracic ratio LVEF (%))

Fig. 3. A scatter plot of left ventricular ejection fraction (LVEF) according to the cardiothoracic ratio. The LVEF and the cardiothoracic ratio show a weak negative correlation. White circles indicate four atypical patients with an LVEF of less than 40 mmHg without cardiomegaly.

**DISCUSSION**

The results of this study showed that the median cardiothoracic ratio in the normal left ventricular systolic function group was 0.54 (interquartile range, 0.50–0.60), and that the traditional abnormal cardiothoracic ratio standard of 0.50 cannot be utilized to
identify impaired ventricular systolic function. A cardiothoracic ratio of 0.50 is typically considered suggestive of cardiomegaly, but our findings indicate the cardiothoracic ratio criterion for prediction of LVSD could be set to 0.56 or greater; however, the AUC for the 0.56 value was less than 0.700. The optimal cardiothoracic ratio presented in this study is therefore not a decisive or absolute standard, but rather a rough indicator of LVSD to be used in conjunction with other diagnostic findings.

To the best of our knowledge, there have been few studies assessing the predictive value of the CT-measured cardiothoracic ratio when diagnosing LVSD. A recent study by Kaiume et al. [17] is especially noteworthy. They reported that the maximum transverse cardiac diameter and CT ratio are useful for detecting LVSD, with AUCs of 0.794 and 0.746, respectively. The Kaiume et al. [17] results are consistent with our finding that the CT-measured cardiothoracic ratio can predict reductions in left ventricular systolic function. Major advantages of the current study as compared with Kaiume et al. [17] are a larger number of patients (83 vs. 39 patients with LVSD), and shorter interval between echocardiography and CT imaging (less than 24 hours vs. 3 months).

The optimal CT-measured cardiothoracic ratios for prediction of mild, moderate, and severe LVSD were found to be 0.56, 0.59, and 0.60, respectively. It is particularly noteworthy that the NPV of the cardiothoracic ratio for LVSD is very high: cardiothoracic ratios of < 0.56, < 0.59, and < 0.60 can predict the absence of LVSD with 90%, 94%, and 98%, respectively. In patients with LVSD, the decision to administer a bolus of intravenous fluids or several important medications with negative inotropic effect (such as β-blockers or calcium channel blockers) should be made judiciously. The high NPV of the cardiothoracic ratio in predicting systolic dysfunction may improve patient care when echocardiography is not immediately available but intravenous fluid or medications with negative inotropic effect are necessary.

The results of this study reaffirmed that it is difficult to accurately predict left ventricular systolic function using the cardiothoracic ratio. Although the moderate and severe LVSD groups had significantly greater cardiothoracic ratios than that of the normal systolic function group, the AUC was not greater than 0.700 no matter which cardiothoracic ratio criteria were used. This result was consistent with the results of the Philbin et al. [18] study that reported the chest radiographic cardiothoracic ratio and LVEF were only slightly negatively correlated, making it difficult to predict LVEF accurately using the cardiothoracic ratio alone, and measurement of left ventricular function required direct measurement using echocardiography. Nonetheless, echocardiography is a labor-intensive test that takes a considerable amount of time even when performed by a skilled expert, and is almost impossible to have performed at night or on holidays. In normal patients, the test time is about 10 to 20 minutes, but if abnormalities are found, echocardiographic scans can take as long as 1 hour [19]. The growing demand for echocardiography has led to wait times of several days even in developed countries. A study in the United Kingdom found that the median wait time for inpatients to undergo an echocardiography was 2 days, the median wait time for outpatients was 8 weeks, and the median waiting time was more than 4 months in 21% of cases [20]. In our hospital, echocardiography is only available during the daytime, and the waiting time for outpatient echocardiography is 7 days. For ED patients, echocardiography is usually done on the same day, but recently the number of cases for whom echocardiography cannot be performed on the day of visit is increasing. Therefore, even though the cardiothoracic ratio cannot replace echocardiography for definitive measurement of the LVEF, the cardiothoracic ratio can be used as a rough indicator of LVSD when echocardiography is not available.

Wingate-Saul et al. [21] reported that when echocardiography is performed based on an increased cardiothoracic ratio, the positive prediction is only 6%. The results of the current study also reaffirmed that the PPV of cardiothoracic ratio in predicting LVSD is low, and no matter what cutoff value was used, the PPV did not exceed 30%. Increased cardiothoracic ratio should not be used as a sole indication for echocardiography.

The limitations of this study are as follows. First, selection bias likely occurred in the process of selecting only patients who had undergone both chest CT and echocardiography in the ED. In fact, the patients selected for this study were mostly elderly patients. Therefore, the results of this study cannot be extended to the young patient group. Second, the interobserver agreement between echocardiographers for LVEF measurement was not assessed. Third, the presence of underlying diseases that can affect the measurement of the cardiothoracic ratio, such as chronic obstructive pulmonary disease, heart failure, previous heart surgery, and use of medications that can affect the LVEF, were not investigated due to the retrospective nature of this study. When inotropic agents have been used, the LVEF is typically enhanced among patients with an elevated cardiothoracic ratio. Therefore, if use of inotropic agents had been investigated and adjusted for in the analyses, the study results would have been more robust. Fourth, although the simplest and most widely used method to investigate LV contractility is measuring LVEF by echocardiography, low ejection fraction and LVSD are not equivalent if there is a change in systemic vascular resistance or effective circulating volume, or if the heart becomes hyperdynamic. However, more accurate methods such as nuclear medicine tests or cardiac magnetic resonance imaging...
imaging were not performed for our study subjects. In this study, we had no choice but to use the LVEF as a means of estimating LVSD. Lastly, the cardiothoracic ratios reported in this study were measured using CT and therefore cannot be applied to cardiothoracic ratio measured using chest radiographs.

In conclusion, there is a significant association between the CT-measured cardiothoracic ratio and LVSD. The optimal cutoff value for CT-measured cardiothoracic ratios suggestive of LVSD was 0.56, which is very different from the traditionally defined of abnormal cardiothoracic ratio of 0.50. The optimal CT-measured cardiothoracic ratios for prediction of mild, moderate, and severe LVSD were 0.56, 0.59, and 0.60, respectively. We suggest a CT-measured cardiothoracic ratio of > 0.56 can be used as a rough indicator of mild LVSD. The CT-measured cardiothoracic ratio had a high NPV for LVSD, and a CT-measured cardiothoracic ratio of < 0.60 can exclude severe LVSD with a high degree of confidence.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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None.

AUTHOR CONTRIBUTIONS

Conceptualization: DHS; Data curation: all authors; Formal analysis: JUN; Visualization: JUN, JHL; Writing–original draft: MC, DHS; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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A combination of the Modified Early Warning Score and the Korean Triage and Acuity Scale as a triage tool in patients with infection

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Objective We evaluated the utility of the Korean Modified Early Warning Score (KMEWS), which combines the Modified Early Warning Score (MEWS) and the Korean Triage and Acuity Scale (KTAS), as a triage tool to screen for infection in patients who visit the emergency department.

Methods We retrospectively reviewed data extracted from electronic medical records. Patients aged ≥ 18 years with an infection who were admitted to the hospital via the emergency department between January 2018 and December 2019 were eligible for inclusion. The KMEWS score was calculated as the sum of the KTAS level and the MEWS score. We generated receiver operating characteristic curves and determined the area under the receiver operating characteristic curve (AUC) for the KMEWS, KTAS, MEWS, and Mortality in Emergency Department Sepsis (MEDS) scales. The primary outcome was septic shock, and secondary outcomes were intensive care unit admission and in-hospital mortality.

Results The AUC values (95% confidence interval) for predicting septic shock were as follows: KMEWS, 0.910 (0.902–0.918); MEWS, 0.896 (0.887–0.904); KTAS score, 0.809 (0.798–0.819); and MEDS, 0.927 (0.919–0.934). The AUC values (95% confidence interval) for predicting in-hospital mortality were as follows: KMEWS, 0.752 (0.740–0.764); MEWS, 0.717 (0.704–0.729); KTAS score, 0.764 (0.752–0.776); and MEDS, 0.844 (0.834–0.854). The AUC values (95% confidence interval) for predicting intensive care unit admission were as follows: KMEWS, 0.826 (0.816–0.837); MEWS, 0.782 (0.770–0.793); KTAS score, 0.821 (0.810–0.831); and MEDS, 0.839 (0.829–0.849).

Conclusion The KMEWS, which is a combination of the MEWS and the KTAS scores, might be a useful triage tool in emergency department patients who present with infection, particularly for predicting septic shock.

Keywords Hospital emergency service; Triage; Septic shock; Mortality; Critical care
INTRODUCTION

Sepsis is an inflammatory disease caused by a reaction of the immune system, which can be life-threatening and is responsible for 20% of all hospital deaths each year [1,2]. In patients with sepsis, early resuscitation and intensive care are associated with a lower mortality rate compared with later resuscitation [3]. Therefore, the recognition of sepsis and the timely initiation of evidence-based protocols are critical [4,5]. However, the diagnosis of sepsis using the Sequential Organ Failure Assessment (SOFA) score is time-consuming in overcrowded emergency departments (EDs) [6]. Several markers for predicting septic shock are known, but most of them require laboratory tests that require time. Therefore, a new tool is required that can predict septic shock early in the triage stage [7–11].

The Modified Early Warning Score (MEWS) is a simple physiological score used to screen patients at risk of clinical deterioration using body temperature, blood pressure, pulse rate, respiratory rate, and level of consciousness values and to allow for the early detection of clinical deterioration and the potential need for a higher level of care (Supplementary Table 1) [12,13]. In Korea, the Korean Triage and Acuity Scale (KTAS) was developed based on the Canadian Triage and Acuity Scale and has been used since 2016. The KTAS is a combination of variables, including vital signs and chief complaints, and serves as a tool for determining the severity of the patients’ condition and the priority for treatment in the ED (Supplementary Table 2) [14,15]. The two scoring systems might have different strengths and weaknesses depending on whether the chief complaints are included and whether the hemodynamic variables are subdivided. Therefore, this study was conducted to investigate whether the Korean Modified Early Warning Score (KMEWS), which combines the MEWS and the KTAS scores, is useful as a triage tool to screen patients with infection in the ED.

METHODS

Ethical statements

The study was approved by the Institutional Review Board of Chungnam National University Hospital (No. 2020-10-059). The need for informed consent was waived because of the retrospective study design and the use of anonymized data. Only clinical data were extracted, and no personal or identifiable information was recorded.

Study design and setting

We retrospectively reviewed data extracted from electronic medical records. The study sample included patients aged ≥ 18 years with infections who were admitted to the hospital via the ED between January 2018 and December 2019 at a tertiary care university hospital with 1,350 beds in Daejeon, Korea. The ED provides medical care to approximately 55,000 patients per year. Patients with missing data were excluded.

The diagnosis of infection was confirmed using the relevant International Classification of Diseases, 10th Revision (ICD-10) codes in the medical records. Patients with any of the following infection-related ICD-10 codes were eligible for enrollment: A00–B99, G00–09, I00–02, I30–33, I38–41, J00–22, J36, J40–J43, J68, J69, J80, J85–J86, K11–12, K35–37, K57, K61, K63, K65, K67, K75, K77.0, K80–81, K83.0, K85, L00–08, M00–03, M86, N10, N12, N13.6, N16.0, N28.84–28.86, N30, N34, N39.0, N41, N45, N61, N70–74, and O91.

Sepsis patients were defined by the presence of two or three of the three quick SOFA (qSOFA) clinical criteria (altered mentation, respiratory rate ≥ 22 breaths/min, and systolic blood pressure ≤ 100 mmHg) [16]. Among patients with sepsis, septic shock was clinically defined as a case where a vasopressor was required to maintain a mean arterial pressure of ≥ 65 mmHg and a serum lactate level > 2 mmol/L (> 18 mg/dL) in the ED or during hospitalization [16].
Data collection and outcome measures
We collected clinical data from the patients’ electronic medical records. The information included age, sex, systolic arterial pressure (mmHg), respiratory rate (breaths/min), body temperature (°C), and mental status. We calculated the Charlson Comorbidity Index, which categorizes the comorbidities of patients based on the ICD diagnosis codes found in the administrative data [17], for each patient. In addition, we calculated the Mortality in Emergency Department Sepsis (MEDS) score, the MEWS score, and the KTAS score [7–9,12,13]. The numbers of points on the KTAS score were 5, 4, 3, 2, or 1 for levels 1, 2, 3, 4, and 5, respectively. The KMEWS was calculated as the sum of the KTAS score and the MEWS score. Since both KTAS and MEWS have initial vital signs, the problem of vital signs over weighting is raised. Thus obtained KMEWS-2 by combining KTAS with the score subtracting the initial vital signs from MEWS. In addition, we divided the participants into septic shock and nonseptic shock groups and conducted intergroup comparisons. The primary outcome of this study was septic shock, and secondary outcomes were intensive care unit (ICU) admission and in-hospital mortality.

Data analysis
Continuous variables are expressed by mean± standard deviation or median (interquartile range, IQR). Continuous variables were analyzed using the Student t-test or the Mann-Whitney U-test, and categorical variables were analyzed using chi-square or Fisher exact tests. A multivariable logistic regression was performed to identify predictive factors for septic shock using variables that had previously been reported to be significantly associated with septic shock.

We generated receiver operating characteristic (ROC) curves and determined the area under the ROC curve (AUC) for individual measures (KMEWS, KTAS, MEWS, and MEDS) that was associated with septic shock, ICU admission, and in-hospital mortality. The AUCs of the models were calculated and tested mutually for significance using DeLong equality tests. In addition, the cutoff value was calculated using the Youden index (Youden’s J statistic). All statistical analyses were performed using the IBM SPSS ver. 19.0 (IBM Corp) and MedCalc ver. 14.8.1 (MedCalc). P-values less than 0.05 were considered statistically significant.

RESULTS
Patient characteristics
We enrolled 19,228 patients during the study period, of which 7,907 patients had infection-related diagnosis at discharge, and 2,814 patients with missing data were excluded. If data such as blood test items, history, and state of consciousness were collected inadequately, they were treated as missing data. Thus, 5,093 patients of these were included in the analysis data set (Fig. 1). Among them, 395 and 4,698 patients were in the septic shock and nonseptic shock groups, respectively.

A comparison of the characteristics of the septic shock group and the nonseptic shock group
Table 1 shows a comparative analysis of two groups, patients without septic shock and patients with septic shock, and their baseline characteristics, laboratory findings, and several infection-related markers. Intergroup comparisons of the septic shock group and the nonseptic shock group showed no significant difference in sex; however, the participants in the septic shock group were older (78 years [IQR, 68–83 years] vs. 61 years [42.0–76.0 years], P < 0.001). In the septic shock group, the systolic arterial pressure was lower than that in the nonseptic shock group (99 mmHg [IQR, 85–127 mmHg] vs. 125 mmHg [111–140 mmHg], P < 0.001), and a higher proportion of patients had an altered mental status (72.4% vs. 6.0%, P < 0.001). The septic shock group had a higher Charlson Comorbidity Index (5 [IQR, 4–6] vs. 2 [IQR, 0–5], P < 0.001). The laboratory results were generally worse in the septic shock group (Table 1). The septic shock group had a significantly higher proportion of patients with KTAS levels 1 or 2 (7.3% vs. 56.1%, P < 0.001) and higher MEWS, KTAS, and KMEWS scores (Table 1).

Fig. 1. A flowchart of the study. Infection-related diagnosis was confirmed using the relevant International Classification of Diseases, 10th Revision codes in the medical records. ED, emergency department.
Variables associated with septic shock upon multivariable logistic regression

A multivariable logistic regression revealed that age, transfer from a long-term care facility, KTAS score, and MEWS score were significantly associated with septic shock (Table 2). The adjusted odds ratio was 2.18 (95% confidence interval [CI], 1.76–2.70) for KTAS and 2.09 (95% CI, 1.93–2.27) for MEWS.

### Table 2. A multivariable logistic regression analysis of the factors associated with septic shock in patients in the emergency department

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% Confidence interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.04</td>
<td>1.03–1.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Long-term care facility (yes)</td>
<td>2.97</td>
<td>2.11–4.17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Korean Triage Acuity Scale score</td>
<td>2.18</td>
<td>1.76–2.70</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Modified Early Warning Score</td>
<td>2.09</td>
<td>1.93–2.27</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### ROC curve analysis

In the ROC analysis, the AUC values (95% CI) of factors associated with septic shock were as follows: KMEWS, 0.910 (0.902–0.918); MEWS, 0.896 (0.887–0.904); KTAS score, 0.809 (0.798–0.819); and MEDS score, 0.927 (0.919–0.934) (Fig. 2). The optimal cutoff value of the KMEWS for predicting septic shock was 7 (AUC, 0.910; sensitivity, 81.3% [95% CI, 77.1%–85.0%]; specificity, 82.6% [95% CI, 81.5%–83.7%]). The respective AUC values (95% CI) of the factors associated with mortality were KMEWS, 0.752 (0.740–0.764); MEWS, 0.717 (0.704–0.729); KTAS score, 0.764 (0.752–0.776); and MEDS, 0.844 (0.834–0.854) (Fig. 3). The respective
AUC values (95% CI) of factors associated with ICU admission were as follows: KMEWS, 0.826 (0.816–0.837); MEWS, 0.782 (0.770–0.793); KTAS score, 0.821 (0.810–0.831); and MEDS, 0.839 (0.829–0.849) (Fig. 4). In addition, the respective AUC values (95% CI) of factors associated with septic shock were as follows: KMEWS, 0.910 (0.902–0.918); MEWS, 0.896 (0.887–0.904); KTAS score, 0.809 (0.798–0.819); and MEDS, 0.927 (0.919–0.934) (Fig. 4). In addition, the respective AUC values (95% CI) of factors associated with septic shock were as follows: KMEWS, 0.910 (0.902–0.918); MEWS, 0.896 (0.887–0.904); KTAS score, 0.809 (0.798–0.819); MEDS, 0.927 (0.919–0.934); and KMEWS-2, 0.894 (0.885–0.902) (Supplementary Fig. 1).

**DISCUSSION**

In this study, the KMEWS, a combination of the MEWS and KTAS scores, was a useful prognostic marker for patients with infection, particularly for predicting septic shock. In the ED, triage helps predict the severity of conditions and determines the priority of patient treatment [18]. The most well-known triage scales are the Emergency Severity Index in the United States, the Canadian Triage and Acuity Scale in Canada, the Australian Triage Scale in Australia, and the Manchester Triage Scale in the United Kingdom [18,19]. In Korea, the KTAS was developed based on the Canadian Triage and Acuity Scale and was implemented in 2015. The KTAS consists of a five-level system that classifies patients using a combination of variables, including vital signs and chief complaints [14,15]. Since the implementation of the KTAS, the admission and disposition patterns have changed and resulted in reduced mortality in the ED [14].

Patients visit the ED with a wide variety of complaints, but the proportion of patients with infection is substantial [20,21]. Because the early diagnosis of sepsis or septic shock is one of the most important factors that affects the success of treatment, many scoring systems that use various markers have been used [22,23]. However, the current triage tools are inadequate for determining the severity and prognosis of patients presenting to the ED with infection [24,25].

The qSOFA score is an established screening tool for sepsis [6]. However, the qSOFA is not suitable as a screening tool because of
its low sensitivity [26]. The MEDS score consists of nine factors that are associated with a greater mortality risk, including an age > 65 years, an altered mental status, and a terminal illness. The MEDS score has moderate accuracy in predicting mortality in ED patients with suspected infection, and the MEDS is superior to the MEWS in predicting mortality in this patient population [7–9]. However, the nine factors that comprise the MEDS score include the platelet count and neutrophil count; since it takes time to obtain the score, it is thus not suitable for use as a triage screening tool in the ED.

The Early Warning Score is a simple physiological scoring system that can be easily applied at the bedside [12]. The MEWS is used as a screening tool for septic shock patients who are at risk of clinical deterioration using the values of temperature, blood pressure, pulse, respiratory rate, and level of consciousness. The MEWS may be useful for screening patients with septic shock [12,13,16,27]. Moreover, the MEWS does not require laboratory test results; therefore, it is immediately available during triage.

However, as the MEWS is somewhat nonspecific and does not contain factors related to the chief complaint, there is a limitation in its use for patients with infection. In contrast, the KTAS includes the chief complaint and the vital signs, but the hemodynamic criteria are not subdivided. The KTAS and MEWS can be applied to ED triage because laboratory results are not required. Therefore, we hypothesized that supplementing the physiological data with the MEWS and KTAS scores could help determine a prompt prognosis in infected patients.

As the KTAS includes both vital signs and chief complaints, and the MEWS includes vital signs, the KMEWS (the sum of the KTAS and the MEWS scores) has a weighting value for the initial vital signs. In the multivariable logistic regression analysis of this study, the KTAS and KMEWS scores were independently associated with septic shock and showed similar odds ratios for septic shock. Therefore, the KMEWS was calculated by combining the two scores. As a result, the KMEWS showed similar or higher AUC values for septic shock, ICU admission, and mortality compared to either the KTAS score or the MEWS score alone. The MEDS had a slightly higher AUC value than the KMEWS, but it is unsuitable for use as a septic shock screening tool in the ED. Therefore, the KMEWS could be a useful prognostic tool for triaging patients with septic shock in the ED.

Nevertheless, this study had some limitations. First, it was a single-center observational study that included only patients admitted to the hospital via the ED. Patients who had been transferred from another hospital or who died in the ED were excluded. Therefore, the generalizability of our results may be limited. Second, it included a collection of retrospective data that could introduce potential information biases and contained much missing data. Third, the sepsis diagnosis process was excluded because it was a retrospective study of patients who had already been diagnosed with an infectious disease. Inclusion criteria in our study were based on ICD-10 codes related to infection, and no blood culture reports were available. The diagnosis of septic shock was defined as sepsis with a serum lactate level > 2 mmol/L, which did not reflect the patient’s volume status. Finally, there could have been inter-clinician variability in calculating the KTAS score and the MEWS score during triage.

The KMEWS, which is a combination of the MEWS and the KTAS scores, could be a useful triage tool for screening patients for septic shock in the ED. In addition, it showed acceptable predictive power for mortality or ICU admission in patients with infection. Prospective multicenter studies are necessary to validate these findings.
SUPPLEMENTARY MATERIALS

Supplementary Fig. 1. Analysis of receiver operating characteristics curves for predicting septic shock.

Supplementary Table 1. Calculation of the Modified Early Warning Score

Supplementary Table 2. Definitions, related conditions, and corresponding medical actions of the Korean Triage and Acuity Scale

Supplementary materials are available at https://doi.org/10.15441/ceem.22.339.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conceptualization: SR; Data curation: SR, SKO; Formal analysis: SKO, BKL; Funding acquisition: SKO; Investigation: SKO, BKL; Methodology: SR, SJ; Project administration: SR, SJ; Resources: SR, SKO; Software: SR, SJ; Supervision: SR, SKO; Validation: SR, SKO; Visualization: SR, BKL; Writing–original draft: SR, SKO, SJ; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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### Supplementary Table 1. Calculation of the Modified Early Warning Score

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<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
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<td>70–80</td>
<td>81–100</td>
<td>101–199</td>
<td>-</td>
<td>≥ 200</td>
<td>-</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>-</td>
<td>&lt; 40</td>
<td>40–50</td>
<td>50–100</td>
<td>101–110</td>
<td>111–129</td>
<td>≥ 130</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min)</td>
<td>-</td>
<td>&lt; 9</td>
<td>-</td>
<td>9–14</td>
<td>15–20</td>
<td>21–29</td>
<td>≥ 30</td>
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<tr>
<td>Temperature (°C)</td>
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<td>&lt; 35</td>
<td>-</td>
<td>35–38.4</td>
<td>-</td>
<td>≥ 38.5</td>
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<td>Reacting to voice</td>
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<td>Unresponsive</td>
<td></td>
</tr>
</tbody>
</table>

AVPU, awake, verbal, pain, unresponsive.
**Supplementary Table 2.** Definitions, related conditions, and corresponding medical actions of the Korean Triage and Acuity Scale

<table>
<thead>
<tr>
<th>Level</th>
<th>Definition</th>
<th>Related condition</th>
<th>Corresponding medical action</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (resuscitation)</td>
<td>Condition poses a threat to the patient's life or extremities</td>
<td>Cardiac arrest, major trauma associated with shock, severe respiratory failure, severely decreased mentation (GCS, 3–8)</td>
<td>Immediate aggressive intervention is required</td>
</tr>
<tr>
<td>II (emergent)</td>
<td>Condition has the potential to put the patient's life, limbs, or body function at risk</td>
<td>Moderate respiratory failure, symptomatic hypertension (SBP &gt; 220 mmHg or DBP &gt; 130 mmHg), moderately decreased mentation (GCS, 9–13), fever (body temperature &gt; 38 °C; SIRS &gt; 3, or SIRS &gt; 2 with suspected infection), severe chest pain, abdominal pain (NRS, &gt; 7), severe headache, major trauma</td>
<td>Early intervention is required</td>
</tr>
<tr>
<td>III (urgent)</td>
<td>Condition can eventually lead to serious complications</td>
<td>Mild respiratory failure, asymptomatic hypertension (SBP &gt; 220 mmHg or DBP &gt; 130 mmHg), vomiting and/or nausea (mild dehydration), moderate abdominal pain (NRS, 4–7), moderate headache (NRS, 4–7), non-controllable bloody diarrhea</td>
<td>Immediate intervention is not necessarily required</td>
</tr>
<tr>
<td>IV (less urgent)</td>
<td>Condition is associated with age, pain, or other related patient complications</td>
<td>Confusion, symptom of urinary infection, constipation (NRS, &lt; 4), mild pain (NRS, &lt; 4)</td>
<td>Intervention or reassessment may be required within 1–2 hr</td>
</tr>
<tr>
<td>V (nonurgent)</td>
<td>Condition is derived from a chronic problem</td>
<td>Mild diarrhea, bite, dressing, drug prescriptions</td>
<td>Examination or intervention can be delayed</td>
</tr>
</tbody>
</table>

GCS, Glasgow Coma Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; SIRS, systemic inflammatory response syndrome; NRS, numeric rating scale.
Supplementary Fig. 1. Analysis of receiver operating characteristics curves for predicting septic shock. The areas under the receiver operating characteristic curve (AUC) of the models were calculated and tested mutually for significance using DeLong equality tests. The Korean Modified Early Warning Score (KMEWS) is the sum of the Korean Triage and Acuity Scale (KTAS) score and the Modified Early Warning Score (MEWS) score. KMEWS-2 is the sum of KTAS with the score subtracting the initial vital sign from MEWS. MEDS, Mortality in Emergency Department Sepsis; CI, confidence interval.

<table>
<thead>
<tr>
<th>Variable</th>
<th>AUC (95% CI)</th>
<th>P-value</th>
<th>P-value (equality compared to KMEWS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KMEWS</td>
<td>0.910 (0.902–0.918)</td>
<td>&lt; 0.001</td>
<td>-</td>
</tr>
<tr>
<td>MEWS</td>
<td>0.896 (0.887–0.904)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>KTAS score</td>
<td>0.809 (0.798–0.819)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MEDS</td>
<td>0.927 (0.919–0.934)</td>
<td>&lt; 0.001</td>
<td>0.019</td>
</tr>
<tr>
<td>KMEWS-2</td>
<td>0.894 (0.885–0.902)</td>
<td>&lt; 0.001</td>
<td>0.027</td>
</tr>
</tbody>
</table>
The role of repeated brain computed tomography based on ultrasound monitoring of optic nerve sheath diameter after moderate traumatic brain injury

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²Modeling in Health Research Center, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran

**Objective** This study was conducted to evaluate the association between changes in repeated brain computed tomography (CT) findings and the optic nerve sheath diameter (ONSD) determined by ocular ultrasonography in patients with moderate blunt traumatic brain injury (TBI).

**Methods** This cross-sectional study was performed on patients with moderate blunt TBI (Glasgow Coma Scale, 9–12) who were referred to the emergency department during a 1-year period. Initially, all patients underwent a brain CT scan and primary ocular ultrasonography. Patients who were candidates for a second brain CT scan under observation in the emergency department also underwent a second ocular ultrasound. The primary outcome was the progression of brain lesions on repeated brain CT scans. Logistic regression and the area under receiver operating characteristic curve (AUC) were used.

**Results** Overall, 204 patients with a mean age of 43 ± 13.4 years were enrolled in the study. The study detected expanding changes in brain CT scans from 29 patients (14.2%). The progression of lesion on CT scan were significantly associated with changes in the Glasgow Coma Scale. In the second brain CT scan, there were significant associations between the progression of lesion on CT scan and the increased size of the ONSD measured on both axial and coronal sections (odds ratio, 17.3–47.5; AUC, 0.88–0.93).

**Conclusion** Among patients with moderate TBI, an increase in ONSD on ocular ultrasound seems to be an appropriate criterion for repeating a brain CT scan to select a suitable therapeutic intervention.

**Keywords** Hospital emergency service; Traumatic brain injuries; Ultrasonography
INTRODUCTION

A brain computed tomography (CT) scan is the first diagnostic imaging procedure for patients with traumatic brain injury (TBI) admitted to the emergency department (ED). It is performed in all patients with moderate TBI. Under certain conditions, conducting a delayed brain CT scan is recommended to assess the progression of brain injury. However, delayed brain CT scans are not indicated in some cases and impose additional costs on the health system and expose patients to some complications. So, along with clinical criteria, it is necessary to develop an accessible, rapid, and safe diagnostic method for estimating the extent of TBIs [1,2].

The ocular ultrasound is used as a diagnostic method to determine intracranial pressure (ICP) by measuring optic nerve sheath diameter (ONSD) [3,4]. Several studies performed to evaluate the applicability of ocular ultrasound findings in assessing the severity of TBI have shown a significant positive correlation between ONSD and ICP [5,6]. Also, the ratio of ONSD to the transverse diameter of the eyeball in the ultrasound can be a significant predictor of changes in ICP [7]. Therefore, ONSD changes seem to be directly related to cerebrospinal fluid pressure changes. Studies have shown that patients with brain lesions and injuries usually have a larger ONSD than individuals without brain damage [8,9].

So, in patients with progressing or newly developed TBI, ONSD changes may indicate the need to repeat brain CT scans and consider therapeutic interventions as soon as possible. This study aimed to investigate the association between changes in repeated brain CT findings and the ONSD determined by ocular ultrasonography in patients with moderate blunt TBI.

METHODS

Ethical statements

This study was approved by the Ethics Committee of the Kerman University of Medical Sciences (No. IR.KMU.AH.REC.1399.180). Before patients entered the study, verbal consent was obtained from each patient’s medical proxy.

Study design

The study was a cross-sectional study on patients with moderate blunt TBI (Glasgow Coma Scale [GCS], 9–12 of 15) referred to the ED, a level II trauma center, during 1 year from March 1, 2020 to March 1, 2021. Inclusion criteria were age over 18 years, having blunt head trauma with a GCS between 9 and 12 (moderate TBI), and consent to participate from the patient’s medical proxy. Exclusion criteria were intubated patients, medical proxy not providing support for participation in the study, age < 18 years, penetrating head trauma, body mass index over 30 kg/m², pregnancy, having eyelid and orbital trauma and optic nerve injuries, emergency conditions requiring immediate transfer of the patient to the operating room, not repeating the brain CT scan, and ED arrival delayed by over 2 hours after injury. First, after arriving and having vital signs recorded, all patients underwent brain CT scans (Asteion 4, Toshiba). Patients then underwent a primary ocular ultrasound administered by an emergency medicine specialist at most 30 minutes after the CT scan. The providers were blinded to the results of the CT scans. The lesions observed on the brain CT scan and the baseline ONSD diameter, as well as other required information, were gathered by an emergency medicine assistant (postgraduate grade year 3) using a questionnaire. In patients who underwent a second brain CT scan based on a neurosurgeon’s counseling, a second ocular ultrasound was performed by the same emergency medicine specialist. According to the results, brain CT scans categorized patients into two groups: those with and without noticeable progression (expanding changes of intracranial lesions). Finally, changes in these two groups in ONSD and other variables were assessed.
Measurements

In both coronal and axial sections, a linear probe (7.5 MHz) with a standard technique of ultrasound machine (MX7, Mindray) was used to determine the ONSD. First, the patients were placed in a supine position. Then their closed eyelids were soaked with a sterile gel. A linear probe was placed transversely over the patient’s closed eyelid to obtain an axial view of the optic nerve. ONSD was measured at 3 mm posterior to the papilla. The probe was placed in a craniocaudal position to determine ONSD in the coronal view. The exact measurements were performed for both eyes [10].

Variables and outcomes

Age, sex, GCS, heart and respiratory rates, and ocular ultrasound findings (the ONSD of right and left eyes in both axial and coronal sections) were recorded. The primary outcome was the progression of brain lesions on repeated brain CT scans. We compared the variables according to the outcome.

Statistical analysis

Continuous variables were analyzed using the Student t-test, and categorical variables were analyzed using the chi-square test. For quantitative variables, mean ± standard deviation was used. Odds ratios and 95% confidence intervals were used to express the association between the severity of the change of ONSD and an expanding change on the brain CT scan. Logistic regression was performed between brain CT scan and ONSD changes. Then the sensitivity, specificity, positive predictive value, negative predictive value, and the area under the curve (AUC) for predicting the need for repeating brain CT scans were calculated for ONSD. A P-value of < 0.05 was considered statistically significant.

RESULTS

Overall, 251 patients with a diagnosis of moderate blunt TBI were admitted to the ED, of whom 47 were excluded, and finally, 204 patients were enrolled in the study (Fig. 1). The mean age of the patients was 43 ± 13.4 years. Regarding sex, 145 patients (71.1%) were male, and 59 patients (28.9%) were female. Brain CT scan findings were normal in 23 patients (11.3%), 17 (8.3%) had skull fractures, 20 (9.8%) had a cerebral hemorrhage, and 144 (70.6%) had mixed lesions (more than one lesion such as intracranial hemorrhage, subdural hematoma, epidural hematoma, subarachnoid hemorrhage, contusion). Expanding changes in brain CT scans were observed in 29 patients (14.2%) (Table 1). The patients were divided into two groups: patients with and without brain CT scan expanding changes. Accordingly, there was a significant relationship between brain CT scan expanding changes and GCS (P = 0.03); however, age, sex, respiratory, and heart rates were not significantly associated with brain CT scan expanding changes. Regarding the first ocular ultrasound, there was no significant relationship between changes in the brain CT scan and ONSD at axial and coronal sections in the right and left eyes. However, regarding the second brain CT scan, there were significant differences between the brain CT scan expanding changes with the increased size of the ONSD of the right and left eyes in both axial and coronal sections (P < 0.01) (Tables 2, 3). In the univariate logistic regression analysis based on increased size of the ONSD, this significant difference was shown. As depicted, there were 47.5 times

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>43.0 ± 13.4</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>145 (71.1)</td>
</tr>
<tr>
<td>Female</td>
<td>59 (28.9)</td>
</tr>
<tr>
<td>Glasgow Coma Scale</td>
<td>10.6 ± 1.2</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>100.7 ± 21.0</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min)</td>
<td>22.5 ± 4.8</td>
</tr>
<tr>
<td>CT scan finding</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>23 (11.3)</td>
</tr>
<tr>
<td>Skull fracture</td>
<td>17 (8.3)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>20 (9.8)</td>
</tr>
<tr>
<td>Mixed</td>
<td>144 (70.6)</td>
</tr>
<tr>
<td>CT scan expanding changes</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>29 (14.2)</td>
</tr>
<tr>
<td>No</td>
<td>175 (85.8)</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number (%).

Fig. 1. Flowchart showing enrollment of patients. TBI, traumatic brain injury; CT, computed tomography.
Table 2. Comparison of clinical variables and ONSD according to the brain CT changes

<table>
<thead>
<tr>
<th>Variable</th>
<th>CT scans expanding changes</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n = 175)</td>
<td>Yes (n = 29)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>43.4 ± 13.3</td>
<td>40.4 ± 13.5</td>
</tr>
<tr>
<td>Sex</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Glasgow Coma Scale</td>
<td>10.7 ± 1.2</td>
<td>10.1 ± 1.1</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>101.0 ± 20.4</td>
<td>99.0 ± 24.5</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min)</td>
<td>22.3 ± 4.8</td>
<td>24.1 ± 4.9</td>
</tr>
</tbody>
</table>

Ocular ultrasonography finding

| First | Coronal ONSD (mm) | Right | 5.6 ± 0.6 | 5.8 ± 0.7 | 0.33       |
|       |                  | Left  | 5.6 ± 0.6 | 5.7 ± 0.8 | 0.36       |
|       | Axial ONSD (mm)  | Right | 6.8 ± 0.6 | 7.0 ± 0.7 | 0.31       |
|       |                  | Left  | 6.7 ± 0.6 | 6.8 ± 0.8 | 0.30       |
| Second| Coronal ONSD (mm)| Right | 5.3 ± 0.5 | 6.7 ± 0.5 | < 0.01     |
|       |                  | Left  | 5.3 ± 0.5 | 6.6 ± 0.5 | < 0.01     |
|       | Axial ONSD (mm)  | Right | 6.5 ± 0.5 | 7.8 ± 0.6 | < 0.01     |
|       |                  | Left  | 6.4 ± 0.5 | 7.7 ± 0.5 | < 0.01     |

Values are presented as mean ± standard deviation.
ONSD, optic nerve sheath diameter.

Table 3. Comparison of CT scan and ONSD changes

<table>
<thead>
<tr>
<th>ONSD changes</th>
<th>CT scans expanding changes</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n = 175)</td>
<td>Yes (n = 29)</td>
</tr>
<tr>
<td>Right coronal</td>
<td></td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Increased</td>
<td>5 (15.6)</td>
<td>27 (84.4)</td>
</tr>
<tr>
<td>No changes</td>
<td>6 (85.7)</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>Decreased</td>
<td>164 (99.4)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Left coronal</td>
<td></td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Increased</td>
<td>7 (20.0)</td>
<td>28 (80.0)</td>
</tr>
<tr>
<td>No changes</td>
<td>32 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Decreased</td>
<td>136 (99.3)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Right axial</td>
<td></td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Increased</td>
<td>4 (13.3)</td>
<td>26 (86.7)</td>
</tr>
<tr>
<td>No changes</td>
<td>3 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Decreased</td>
<td>168 (98.2)</td>
<td>3 (1.8)</td>
</tr>
<tr>
<td>Left axial</td>
<td></td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Increased</td>
<td>12 (30.0)</td>
<td>28 (70.0)</td>
</tr>
<tr>
<td>No changes</td>
<td>10 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Decreased</td>
<td>149 (99.3)</td>
<td>1 (0.7)</td>
</tr>
</tbody>
</table>

Values are presented as number (%).
CT, computed tomography; ONSD, optic nerve sheath diameter.

The odds of brain CT scan expanding changes in the patients with increased ONSD on the left coronal section. Other sonographic sections showing significant associations with changes on the brain CT are also noted (P < 0.01) (Table 4). To determine the cutoff for the desired variables, we first performed logistic regression and then calculated the sensitivity and specificity for different cutoffs and selected the cutoff (0.5 mm) that had the highest sensitivity and specificity. Finally, both axial and coronal sections were used to calculate the sensitivity, specificity, positive predictive value, negative predictive value, and AUC of ONSD for the right and left eyes. The best results were related to the left coronal section for sensitivity, specificity, positive predictive value, negative predictive value, and AUC of ONSD (97.8%, 89.6%, 63.2%, 99.6%, 0.93, respectively) (Table 5).

DISCUSSION

This study investigated the value of ONSD obtained on ocular ultrasonography for the need to repeat a brain CT scan in patients with moderate blunt head TBI. Our results indicate that patients with a difference between the first and second ONSD might have a potential for the progression of the brain injury or the development of a new severe brain injury. Therefore, repeat head CT is recommended in these patients. Also, a decrease in GCS should be an indication for repeating the brain CT scan for these patients.

The optic nerve is part of the central nervous system. It is surrounded by the subarachnoid cerebrospinal fluid and dura mater. In the case of increased ICP, the size of the ONSD also increases.

The optic ultrasonography of the ONSD is a simple, noninvasive, and safe method for estimating cerebral ICP that can be an excellent alternative to invasive approaches. As a diagnostic method, ONSD
Repeated brain CT in moderate TBI patients based on ONSD measurement in patients with head trauma by ocular ultrasound was introduced years ago. Measurements are performed with a linear probe 3 mm behind the optic disc, in which the presence of a hypoechoic structure with a size of up to 5 mm is normal; nevertheless, a size above 5.7 mm indicates intracerebral hypertension [11]. Changes in ONSD correlate with ICP variations, so increased ICP (in conditions such as cerebral edema) is associated with elevated ONSD. On the other hand, ONSD decreases in situations where ICP is reduced (e.g., hyperventilation) [12,13]. Therefore, in patients with head trauma, the constant monitoring of ONSD by ocular ultrasonography can help monitor ICP and determine the prognosis of these patients. In one study, patients with reduced ONSD had a good prognosis and usually did not need surgery [14]. In addition to predicting ICP changes, ONSD dynamic changes may help predict bleeding volume and even the outcome in intracranial hemorrhage (ICH) patients. Their study showed that the size of ONSD increases with bleeding volume in ICH patients. Their study showed that an ONSD size greater than 0.66 mm on an ocular ultrasound could predict a cerebral hemorrhage of more than 2.5 cm³, with a diagnostic accuracy of >90% [15]. In another study, Bender et al. [16] repeatedly measured ONSD by ocular ultrasound in patients with exacerbating clinical conditions, who often underwent brain CT scans. Their study showed that patients with elevated ONSD had worse outcomes. They also found significant relationships between elevated ONSD and decreased GCS and ICH bleeding volume [16]. Naldi et al. [17] also declared in their study that ICH patients had greater ONSD values than individuals without cerebral hemorrhage. Considering the correlation between ONSD and ICP changes, ocular ultrasound could be a reliable tool for monitoring patients with cerebral hemorrhage [9]. In our study, we also found a significant relationship between ONSD size in ocular ultrasound and either newly developed lesions or the progression of incremental lesions observed in brain CT scans. This means that the patients who showed signs of new injuries in the brain CT scan also had elevated ONSD on ocular ultrasound, suggesting the need to repeat the brain CT scan. Overall, ONSD monitoring in the ED can be beneficial for the rapid diagnosis of brain injury. In their study, Guzeldag et al. [18] showed a significant inverse correlation between ONSD and GCS, meaning that with decreasing GCS, there was an increase in the size of ONSD. Consistently, we also showed that the patients who developed new brain injuries or revealed deterioration in brain CT scans also had a decline in GCS, which could be a criterion for repeating the scan. Several studies in this field align with our research [19–21].

The limitations of this study include being a single-center study, not including patients with severe TBI, pregnant women, obese patients, and those under 18 years of age, and the fact that some patients’ medical proxies did not give consent for participation.

In conclusion, ocular ultrasonography of ONSD can help monitor patients with moderate blunt TBI in the ED. In these patients, increased ONSD on ocular ultrasound appears to be an appropriate criterion for repeating a brain CT scan and performing appropriate therapeutic interventions.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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None.

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AUTHOR CONTRIBUTIONS

Conceptualization: AM, MT; Data curation: AM; Formal analysis: MM; Methodology: all authors; Resources: MT, AM; Software: MT, MM; Supervision: AM, MT; Visualization: AM, MT; Writing–original draft: MT; Writing–review & editing: MT, MM. All authors read and approved the final manuscript.

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REFERENCES


Serum phosphate is not an early predictor of neurocognitive outcomes in acute carbon monoxide poisoning patients

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³Research Institute of Hyperbaric Medicine and Science, Yonsei University Wonju College of Medicine, Wonju, Korea

**Objective** Carbon monoxide (CO) poisoning causes brain injury by hypoxia and inflammatory mechanisms. Hypoxic conditions result in increased serum phosphate concentration due to loss of polarity of the cell membrane, changes in membrane fluidity, and consequent destruction of phospholipids in the cell membrane. This study aimed to evaluate whether serum phosphate measured in the emergency department (ED) can serve as an early predictor of neurocognitive sequelae 1 month after acute CO poisoning.

**Methods** We included patients ≥ 16 years with acute CO poisoning from a cohort who were treated at a single tertiary academic hospital in Wonju, Korea, between January 2006 and May 2021. Neurocognitive outcome was assessed using the Global Deterioration Scale score; patients were classified into favorable (1–3 points) or poor (4–7 points) neurocognitive outcome groups based on this score. These two groups were compared before and after propensity score matching.

**Results** Data from 888 patients were analyzed. Seven hundred seventy-one patients (86.8%) were assigned to the favorable outcome group and 117 patients (13.2%) to the poor outcome group. Patients with a poor outcome had a higher mean serum phosphate level than those with a favorable outcome (3.9 mg/dL vs. 3.5 mg/dL, P = 0.001). Propensity score matching yielded 85 matched patient pairs. After matching, serum phosphate level in the ED was not significantly different between the favorable and poor outcome groups (3.9 vs. 3.7 mg/dL, P = 0.349).

**Conclusion** Serum phosphate level measured in the ED did not predict poor neurocognitive outcomes 1 month after CO poisoning.

**Keywords** Carbon monoxide poisoning; Phosphates; Cognitive dysfunction; Propensity score
INTRODUCTION

Carbon monoxide (CO) poisoning causes tissue hypoxia due to its affinity for hemoglobin, in addition to direct inflammatory damage to tissues through various mechanisms [1,2]. CO binds competitively to heme-containing proteins such as hemoglobin and myoglobin as well as mitochondrial cytochrome c oxidase (complex IV), resulting in tissue hypoxia [1]. Therefore, CO poisoning damages organs that are heavily reliant on oxygen such as the brain, heart, and muscles [3].

Patients with neurocognitive sequelae caused by CO poisoning may present with symptoms such as mental deterioration, cognitive dysfunction, amnesia, gait disturbance, mutism, urinary or fecal incontinence, psychosis, depression, and Parkinsonism [2,4–6]. Hyperbaric oxygen therapy (HBO2) within 24 hours after poisoning is recommended for symptomatic patients with CO poisoning based on previous randomized control trials [7,8]. Weaver et al. [8] reported that HBO2 use (compared to nonuse) in patients with CO poisoning reduced neurocognitive sequelae at 6 weeks. However, neurocognitive sequelae developed in 25% of patients with acute CO poisoning even with HBO2 use. Therefore, it is important to be able to predict poor neurocognitive outcomes in patients with acute CO poisoning. Patients at high risk for neurocognitive sequelae must be screened for follow-up to allow for early initiation of rehabilitative interventions [9]. In addition, early prediction of poor neurocognitive outcomes would help clinicians plan monitoring and treatment strategies [10].

Various biomarkers for neurocognitive prognosis in CO poisoning patients have been explored, including serum S100ß protein [11,12], neuron-specific enolase [13], and myelin basic protein in cerebrospinal fluid [14]. However, while these tests can predict prognosis, they are difficult to apply in the emergency department (ED).

Phospholipids, a major element of cell membranes and nucleic acids, contain phosphate groups, and phosphate-containing compounds play essential roles in multiple physiological processes including cellular signal transduction, mineral metabolism, and energy exchange [10]. Previous studies have reported that ischemic or hypoxic conditions result in loss of polarity of the cell membrane, changes in membrane fluidity, and consequently destruction of phospholipids in the cell membrane, resulting in increased phosphorus concentrations in blood [15,16]. In addition, under ischemic conditions, inefficient adenosine triphosphate production by anaerobic metabolism increases the level of inorganic phosphate, leading to an increase in serum phosphate [17,18]. Given the positive relationship between phosphate levels and the severity of ischemic injury in conditions such as intestinal ischemia, myocardial infarction, and cardiac arrest [19–25], it is plausible that higher phosphate levels may be associated with poorer outcomes in acute CO poisoning patients by reflecting the severity of hypoxic stress.

We hypothesized that higher serum phosphate levels assessed in the ED would correlate with worse neurocognitive outcomes in patients with CO poisoning. No previous studies have investigated the clinical usefulness of serum phosphate as an early predictor of poor neurocognitive outcomes in patients with acute CO poisoning. Therefore, the aim of this study was to evaluate the ability of serum phosphate measured in the ED to serve as a biomarker for early prediction of neurocognitive sequelae 1 month after acute CO poisoning.

METHODS

Ethical statements

The study was approved by the Institutional Review Board of Wonju Severance Christian Hospital (No. CR319133) and com-
plied with the ethical guidelines of the Declaration of Helsinki. Informed consents were obtained from the patients and we anonymized patient data before the analyses.

**Study design and setting**

The data used in our study were derived from a cohort treated at a single tertiary academic hospital in Wonju, Korea. In January 2006, a CO poisoning registry was opened to prospectively collect patient data in our hospital. Data from January 2006 to July 2020 were obtained from this registry, and data after August 2020 were collected prospectively with informed consent for the CARE CO cohort (ClinicalTrials.gov identifier: NCT04490317). We analyzed data collected between January 2006 and May 2021.

The following criteria were used for exclusion: (1) less than 16 years old, (2) previous CO poisoning history, (3) a history of previous neurocognitive dysfunction such as stroke, dementia, or Parkinson’s disease before acute CO poisoning, (4) specific additive treatment such as therapeutic hypothermia or steroids, (5) serious illness such as advanced cancer, (6) insufficient data for important variables including serum phosphate, (7) preexisting parathyroid disease, as this could influence phosphate levels, (8) failure to follow-up neurocognitive status after discharge, and (9) fire as the CO source.

In our institution, acute CO poisoning is diagnosed based on the patient’s medical history and carboxyhemoglobin (COHb) > 5% (for smokers, > 10%). We treated patients with CO poisoning with 100% oxygen therapy through a face mask with a reservoir bag. Patients with any interval of loss of consciousness, neurocognitive symptoms or signs, cardiovascular dysfunction, elevated cardiac enzymes, ischemic electrocardiogram changes, severe acidosis, or COHb ≥ 25% were treated with HBO₂. [26].

**Study variables and definitions**

We evaluated the following clinical variables in CO poisoning patients: age, sex, intentionality of poisoning, source of CO (charcoal, oil, or gas), drug coingestion, maximal CO exposure time, initial Glasgow Coma Scale (GCS) at the site of rescue or ED arrival, comorbidities (diabetes mellitus, hypertension, cardiovascular diseases, and psychiatric diseases), alcohol coingestion, current smoker, symptoms and signs (loss of consciousness, shock, and seizure), and use of HBO₂. Shock was defined as use of a vasopressor and lactate level greater than 2 mmol/L [27]. CO exposure duration was the estimated maximum duration of CO exposure measured from the time of normal consciousness to patient detection.

Laboratory parameters collected were serum COHb, bicarbonate, lactate, creatinine kinase, troponin I, and phosphate measured within 1 hour of ED arrival. Other electrolytes (sodium, potassium, calcium, and chloride) and variables that could affect phosphate levels (creatinine and albumin) were also measured [28]. In our institution, serum phosphate level is measured during routine laboratory tests using Atellica Solution IM analyzers or Atellica Solution CH analyzers (Siemens Healthineers).

Neurocognitive outcome was assessed using the Global Deterioration Scale (GDS) [29] during a rehabilitation outpatient visit. This scale was also used to determine the prognosis of patients with CO poisoning [30–32]. If the patient was unable to visit the outpatient department due to deteriorated condition, the patient’s caregivers were interviewed. GDS scores range from 1 to 7, where a higher score indicates a more severe condition (Supplementary Method 1 and Supplementary Table 1). GDS scores were classified as favorable (1–3 points) or poor (4–7 points) [30–32]. If a patient died from CO poisoning (CO-related death) within 1 month, a GDS score of 7 was assigned. Patients who died of causes unrelated to CO poisoning were considered to have missing GDS values and were thus excluded from the analyses.

**Statistical analysis**

Summary statistics are reported as mean ± standard deviation for numerical variables and as number (%) for categorical variables. Continuous data were compared using independent t-tests or Mann–Whitney U-tests, while categorical data were compared using Pearson chi-square tests or Fisher exact tests. The Shapiro–Wilks test was used to determine whether continuous variables were normally distributed.

To reduce the effect of selection bias and potential confounders, we used propensity score matching (PSM) to adjust for significantly different variables combined with clinically important variables related to the severity of CO poisoning (age, CO exposure time, GCS, diabetes mellitus, hypertension, loss of consciousness, shock, seizure, bicarbonate, lactate, creatinine, creatine kinase, and troponin I levels) [33]. However, when many variables are included in propensity score matching, it is difficult to match covariates [34]. For balanced matching, we used a greedy matching algorithm (without replacement) with a caliper width of 0.05 standard deviations of the log odds of the estimated propensity score [35], and performed 1:1 matching rather than 1:n matching [36]. After all PSM procedures were performed, we compared baseline covariates between groups. Continuous variables were compared using paired t-tests or Wilcoxon signed-rank tests, as appropriate, and categorical variables were compared using McNemar tests. Univariable linear regression was performed to assess if there was a linear relationship between GDS score and serum phosphate level. The relationship between serum phosphate level and
neurocognitive outcomes was assessed using two multivariable logistic regression models. Models 1 and 2 were adjusted by matching variables and variables found to be significant in univariate analysis, respectively.

All reported P-values are two-sided, and P-values < 0.05 were considered statistically significant. SAS ver. 9.4 (SAS Institute Inc), and R ver. 3.6.3 (R Foundation for Statistical Computing) were used for statistical analyses.

RESULTS

Characteristics of the study population

Among the 1,790 patients with acute CO poisoning, 888 patients were finally included in this study (Fig. 1). According to the 1-month GDS results, patients were divided into two groups: a favorable outcome group (771 patients, 86.8%) and a poor outcome group (117 patients, 13.2%).

Baseline characteristics of included patients according to outcome are shown in Table 1. Patients with a poor outcome were older than those with a favorable outcome. Additionally, patients with poor outcome had longer CO exposure times and lower GCS scores. The poor outcome group had more patients with diabetes mellitus and hypertension than the favorable outcome group. Furthermore, poor outcome patients were more likely to have experienced loss of consciousness, shock, or seizure. Laboratory results are also shown in Table 1. Patients with a poor outcome had higher levels of lactate, creatinine, creatine kinase, troponin I, phosphate, sodium, and potassium than those with a favorable outcome. Bicarbonate and calcium levels were higher in patients with favorable outcomes.

We investigated whether the 1-month GDS score changed after 1 year (86 patients were lost to follow-up at 1 year). The GDS score of 674 patients of 802 patients (84.0%) remained unchanged. Eighteen patients (2.3%) had an improved GDS score while 20 patients (13.7%) had a worse GDS score.

Characteristics of patients matched based on propensity scores

After performing 1:1 PSM with 13 covariates for the entire population, we obtained 85 matched patient pairs. The balance of co-
Table 1. Baseline characteristics of the propensity score matched and unmatched cohorts

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Unmatched (Favorable outcome n = 771)</th>
<th>Unmatched (Poor outcome n = 117)</th>
<th>Matched (Favorable outcome n = 85)</th>
<th>Matched (Poor outcome n = 85)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>47.4 ± 16.0</td>
<td>57.9 ± 17.0</td>
<td>54.9 ± 16.4</td>
<td>55.8 ± 17.6</td>
<td>0.725</td>
</tr>
<tr>
<td>Male sex</td>
<td>493 (63.9)</td>
<td>66 (56.4)</td>
<td>60 (70.6)</td>
<td>49 (57.7)</td>
<td>0.110</td>
</tr>
<tr>
<td>Intentionality</td>
<td>320 (41.5)</td>
<td>54 (46.2)</td>
<td>36 (42.4)</td>
<td>43 (50.6)</td>
<td>0.282</td>
</tr>
<tr>
<td>Source</td>
<td></td>
<td>0.018</td>
<td></td>
<td></td>
<td>0.599</td>
</tr>
<tr>
<td>Charcoal</td>
<td>647 (83.9)</td>
<td>108 (92.3)</td>
<td>76 (89.4)</td>
<td>78 (91.8)</td>
<td></td>
</tr>
<tr>
<td>Gas</td>
<td>124 (16.1)</td>
<td>9 (7.7)</td>
<td>9 (10.6)</td>
<td>7 (8.2)</td>
<td></td>
</tr>
<tr>
<td>Drug coinfection</td>
<td>60 (7.8)</td>
<td>12 (10.3)</td>
<td>11 (12.9)</td>
<td>9 (10.6)</td>
<td>0.634</td>
</tr>
<tr>
<td>CO exposure time (hr)</td>
<td>5.3 ± 4.5</td>
<td>9.1 ± 4.8</td>
<td>8.0 ± 4.3</td>
<td>8.1 ± 4.7</td>
<td>0.849</td>
</tr>
<tr>
<td>GCS score</td>
<td>13.1 ± 2.9</td>
<td>9.1 ± 3.6</td>
<td>9.7 ± 3.8</td>
<td>10.0 ± 3.4</td>
<td>0.549</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>77 (10.0)</td>
<td>19 (16.2)</td>
<td>10 (11.8)</td>
<td>11 (12.9)</td>
<td>0.816</td>
</tr>
<tr>
<td>Hypertension</td>
<td>136 (17.6)</td>
<td>36 (30.8)</td>
<td>23 (27.1)</td>
<td>26 (30.6)</td>
<td>0.612</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>30 (3.9)</td>
<td>5 (4.3)</td>
<td>5 (5.9)</td>
<td>3 (3.5)</td>
<td>0.469</td>
</tr>
<tr>
<td>Psychiatric disease</td>
<td>98 (12.7)</td>
<td>19 (16.2)</td>
<td>18 (21.2)</td>
<td>15 (17.7)</td>
<td>0.561</td>
</tr>
<tr>
<td>Alcohol</td>
<td>303 (39.3)</td>
<td>34 (29.1)</td>
<td>36 (42.4)</td>
<td>28 (32.9)</td>
<td>0.205</td>
</tr>
<tr>
<td>Current smoker</td>
<td>317 (41.1)</td>
<td>33 (28.2)</td>
<td>34 (40.0)</td>
<td>27 (31.8)</td>
<td>0.263</td>
</tr>
<tr>
<td>Time from rescue to ED arrival (hr)</td>
<td>3.5 ± 3.1</td>
<td>3.8 ± 3.1</td>
<td>3.7 ± 3.2</td>
<td>3.8 ± 3.0</td>
<td>0.815</td>
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<tr>
<td>Symptoms and signs in the ED</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss of consciousness</td>
<td>441 (57.2)</td>
<td>107 (91.5)</td>
<td>74 (87.1)</td>
<td>75 (88.2)</td>
<td>0.816</td>
</tr>
<tr>
<td>Shock</td>
<td>22 (2.9)</td>
<td>14 (12.0)</td>
<td>9 (10.6)</td>
<td>8 (9.4)</td>
<td>0.798</td>
</tr>
<tr>
<td>Seizure</td>
<td>9 (1.2)</td>
<td>8 (6.8)</td>
<td>5 (5.9)</td>
<td>5 (5.9)</td>
<td>1.000</td>
</tr>
<tr>
<td>Use of HBO_{2}</td>
<td>709 (92.0)</td>
<td>100 (85.4)</td>
<td>72 (84.7)</td>
<td>75 (88.2)</td>
<td>0.501</td>
</tr>
<tr>
<td>Laboratory findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COHb (%)</td>
<td>22.1 ± 14.4</td>
<td>23.8 ± 15.3</td>
<td>27.3 ± 16.6</td>
<td>23.8 ± 14.6</td>
<td>0.141</td>
</tr>
<tr>
<td>Phosphate (mg/dL)</td>
<td>3.5 ± 1.1</td>
<td>3.9 ± 1.3</td>
<td>3.9 ± 1.7</td>
<td>3.7 ± 1.3</td>
<td>0.349</td>
</tr>
<tr>
<td>Bicarbonate (mmol/L)</td>
<td>20.7 ± 3.7</td>
<td>18.5 ± 4.2</td>
<td>18.5 ± 4.0</td>
<td>18.7 ± 4.3</td>
<td>0.739</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>2.9 ± 2.4</td>
<td>3.8 ± 3.2</td>
<td>3.8 ± 3.0</td>
<td>3.9 ± 3.4</td>
<td>0.828</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.9 ± 0.3</td>
<td>1.2 ± 0.7</td>
<td>1.08 ± 0.46</td>
<td>1.09 ± 0.49</td>
<td>0.886</td>
</tr>
<tr>
<td>Creatine kinase (μU/L)</td>
<td>987.5 ± 3,281.7</td>
<td>4,422.9 ± 5,323.2</td>
<td>3,036.3 ± 6,094.2</td>
<td>3,648.6 ± 5,078.7</td>
<td>0.478</td>
</tr>
<tr>
<td>Troponin I (ng/mL)</td>
<td>1.0 ± 3.7</td>
<td>4.8 ± 8.1</td>
<td>4.4 ± 8.5</td>
<td>3.6 ± 6.1</td>
<td>0.511</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.4 ± 0.4</td>
<td>4.2 ± 0.4</td>
<td>4.2 ± 0.4</td>
<td>4.2 ± 0.5</td>
<td>0.629</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>140.0 ± 3.1</td>
<td>140.8 ± 3.5</td>
<td>140.0 ± 3.9</td>
<td>141.0 ± 3.5</td>
<td>0.104</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.1 ± 0.5</td>
<td>4.3 ± 0.6</td>
<td>4.2 ± 0.6</td>
<td>4.2 ± 0.6</td>
<td>0.688</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>8.9 ± 0.5</td>
<td>8.8 ± 0.6</td>
<td>8.8 ± 0.6</td>
<td>8.8 ± 0.6</td>
<td>0.732</td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
<td>105.9 ± 3.9</td>
<td>106.7 ± 4.3</td>
<td>106.6 ± 4.8</td>
<td>107.0 ± 4.6</td>
<td>0.646</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number.
CO, carbon monoxide; GCS, Glasgow Coma Scale; ED, emergency department; HBO_{2}, hyperbaric oxygen therapy; COHb, carboxyhemoglobin.

There were no significant differences between favorable and poor outcome groups for any covariate after PSM (Table 1).

Main outcomes for the matched cohorts
Table 1 and Fig. 2 show comparisons of serum phosphate level according to neurocognitive outcomes 1 month post-CO exposure in the overall matched cohort. There was no significant difference in serum phosphate level between the favorable and poor outcome groups (P = 0.349). Additionally, serum phosphate did not have statistically significant linear trend at 1 month after CO poisoning (β = 0.017, P = 0.515) (Fig. 3). The odds ratio for a poor GDS (≥ 4) at 1 month according to serum phosphate level showed a significantly increasing trend for serum phosphate levels of 3 mg/dL or higher. However, after matching, the odds ratio tended to decrease and there were no significant differences for any of the serum phosphate intervals (Fig. 4).

Additional analyses
We performed additional analysis to evaluate the ability of serum...
phosphate level to predict neurocognitive sequelae at an early stage after CO poisoning. In multivariable logistic regression models, serum phosphate was not a significant predictor of a poor prognosis (Table 2). In addition, in the cohort matched based on variables without laboratory tests unrelated to CO exposure (bicarbonate, lactate, creatinine, creatine kinase, and troponin I), serum phosphate was not a significant predictor of poor neurocognitive outcomes (Table 3).

**DISCUSSION**

In this study, serum phosphate level was significantly higher in those patients with a poor outcome before PSM. However, serum phosphate level did not show a significant association with a poor outcome after PSM for factors related to the severity of CO poisoning. In addition, serum phosphate was not a significant predictor of poor outcome in multivariable logistic regression models. This means that serum phosphate level alone cannot predict a poor outcome 1 month after acute CO poisoning. A few studies have reported increased serum phosphate levels in various hypoxia-related diseases. In cardiac arrest patients, serum phosphate is known to be related to prognosis [10,20,23]. High phosphate levels have also been reported in patients with intestinal ischemia [37,38], and correlations between serum phosphate levels and morbidity and mortality in coronary artery disease patients have been reported [25,28,39]. However, despite years of study, use of serum phosphate level for early diagnosis of acute intestinal ischemia is still controversial and is not a routine diagnostic test [40].

We attribute the fact that serum phosphate was not useful for predicting the prognosis of acute CO poisoning patients to the following factors. First, serum phosphate is known to be elevated according to the degree of hypoxia. However, the hypoxic insult of acute CO poisoning may not be as severe as that of cardiac arrest in which severe ischemia occurs due to complete blockage of oxygen supply. That is, the hypoxia of CO may not be severe enough to result in significant changes in laboratory variables. Second, the known pathophysiology of acute CO poisoning involves not
only hypoxia but also inflammatory reactions such as platelet-neutrophil activation, oxidative stress, and cell apoptosis [1,2], which serum phosphate levels do not reflect. Serum phosphate level in addition to laboratory parameters related to the inflammation associated with acute CO poisoning may result in a better predictive model. Third, it takes time for serum phosphate levels to rise after the onset of ischemia, but it is unclear what the appropriate timing is for phosphate measurement to reflect hypoxic damage. In some studies, elevated serum phosphate levels were reported starting within 1 hour of intestinal ischemia [19,42]. However, other studies reported an increase in serum phosphate levels only 3 to 4 hours after ischemia [24,43]. In an intestinal ischemia study, phosphate levels measured in the early stage of ischemia were not significantly different from baseline, but there was a significant increase in irreversible intestinal necrosis due to persistent ischemia [24]. In the current study, considering the relatively short CO-related hypoxic times and the differences in timing of blood collection for the serum phosphate test after CO

| Table 2. Multivariable logistic regression analysis to evaluate predictors of a poor neurocognitive prognosis |
|---|---|---|---|
| Variable | Univariable | Model 1 | Model 2 |
| OR (95% CI) | OR (95% CI) | OR (95% CI) | P-value | P-value |
| Age (yr) | 1.04 (1.03–1.05) | 1.05 (1.03–1.06) | 1.04 (1.02–1.06) | < 0.001 | < 0.001 | < 0.001 |
| Male sex | 0.73 (0.49–1.08) | 0.117 | - | - | - | - |
| Intentionality | 1.21 (0.82–1.79) | 0.343 | - | - | - | - |
| Source | Charcoal | Reference | Reference | Reference | Reference | Reference |
| Gas | 0.44 (0.22–0.88) | 0.021 | - | - | 0.50 (0.20–1.25) | 0.137 |
| Drug coingestion | 1.36 (0.71–2.60) | 0.362 | - | - | - | - |
| CO exposure time (hr) | 1.17 (1.13–1.22) | 0.001 | 1.13 (1.07–1.19) | 0.001 | 1.12 (1.06–1.19) | 0.001 |
| GCS score | 0.74 (0.7–0.78) | 0.001 | 0.79 (0.73–0.86) | 0.001 | 0.80 (0.73–0.87) | 0.001 |
| Comorbidities | Diabetes mellitus | 1.75 (1.01–3.01) | 0.045 | 0.88 (0.44–1.80) | 0.732 | 0.91 (0.43–1.89) | 0.790 |
| Hypertension | 2.08 (1.34–3.20) | 0.001 | 1.11 (0.61–2.00) | 0.739 | 1.01 (0.55–1.84) | 0.980 |
| Cardiovascular disease | 1.10 (0.42–2.90) | 0.843 | - | - | - | - |
| Psychiatric disease | 1.33 (0.78–2.27) | 0.294 | - | - | - | - |
| Alcohol | 0.63 (0.41–0.97) | 0.035 | - | - | 0.95 (0.51–1.76) | 0.880 |
| Current smoker | 0.56 (0.37–0.86) | 0.008 | - | - | 0.74 (0.39–1.37) | 0.332 |
| Time from rescue to ED arrival (hr) | 1.03 (0.97–1.09) | 0.375 | - | - | - | - |
| Symptoms and signs at the ED | Loss of consciousness | 8.01 (4.12–15.55) | < 0.001 | 2.27 (1.00–5.16) | 0.052 | 2.13 (0.93–4.89) | 0.074 |
| Shock | 4.63 (2.30–9.33) | < 0.001 | 1.05 (0.43–2.57) | 0.918 | 1.28 (0.49–3.35) | 0.609 |
| Seizure | 6.21 (2.35–16.45) | 0.000 | 1.36 (0.40–4.64) | 0.621 | 1.32 (0.38–4.63) | 0.663 |
| Use of HBO | 0.51 (0.29–0.92) | 0.024 | - | - | 0.71 (0.32–1.58) | 0.404 |
| Laboratory findings | COHb (%) | 1.01 (1.00–1.02) | 0.248 | - | - | - | - |
| Bicarbonate (mmol/L) | 0.88 (0.84–0.92) | < 0.001 | 0.98 (0.9–1.07) | 0.636 | 1.00 (0.92–1.10) | 0.946 |
| Lactate (mmol/L) | 1.12 (1.05–1.19) | 0.001 | 0.95 (0.84–1.07) | 0.387 | 0.98 (0.86–1.12) | 0.765 |
| Creatinine (mg/dL) | 4.67 (2.97–7.33) | < 0.001 | 2.22 (1.19–4.15) | 0.012 | 2.49 (1.29–4.82) | 0.007 |
| Creatine kinase (U/L) | 1.00 (1.00–1.00) | < 0.001 | 1.00 (1.00–1.00) | 0.005 | 1.00 (1.00–1.00) | 0.010 |
| Troponin I (ng/mL) | 1.11 (1.08–1.15) | < 0.001 | 1.02 (0.98–1.06) | 0.369 | 1.01 (0.97–1.05) | 0.628 |
| Phosphate (mg/dL) | 1.29 (1.12–1.48) | 0.001 | 0.84 (0.68–1.04) | 0.113 | 0.81 (0.65–1.02) | 0.068 |
| Albumin (g/dL) | 0.36 (0.22–0.59) | < 0.001 | - | - | 0.64 (0.29–1.40) | 0.263 |
| Sodium (mmol/L) | 1.09 (1.03–1.17) | 0.007 | - | - | 1.07 (0.99–1.16) | 0.088 |
| Potassium (mmol/L) | 2.08 (1.47–2.96) | < 0.001 | - | - | 1.14 (0.69–1.87) | 0.605 |
| Calcium (mg/dL) | 0.60 (0.42–0.86) | 0.005 | - | - | 1.23 (0.70–2.17) | 0.472 |
| Chloride (mmol/L) | 1.05 (1.00–1.10) | 0.058 | - | - | - | - |

Model 1 was adjusted for statistically significant and clinically important variable not including electrolytes variables. Model 2 was adjusted for significant variables from all variables.

OR, odds ratio; CI, confidence interval; CO, carbon monoxide; GCS, Glasgow Coma Scale; ED, emergency department; HBO, hyperbaric oxygen therapy; COHb, carboxyhemoglobin.
Table 3. Baseline characteristics of cohorts by the propensity score matching without laboratory variables

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Favorable (n=85)</th>
<th>Poor outcome (n=85)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>54.9 ± 16.4</td>
<td>55.8 ± 17.6</td>
<td>0.725</td>
</tr>
<tr>
<td>Male sex</td>
<td>60 (70.6)</td>
<td>49 (57.7)</td>
<td>0.079</td>
</tr>
<tr>
<td>Intentionality</td>
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<td>0.282</td>
</tr>
<tr>
<td>Source</td>
<td></td>
<td></td>
<td>0.599</td>
</tr>
<tr>
<td>Charcoal</td>
<td>76 (89.4)</td>
<td>78 (91.0)</td>
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</tr>
<tr>
<td>Gas</td>
<td>9 (10.6)</td>
<td>7 (8.2)</td>
<td></td>
</tr>
<tr>
<td>Drug coingestion</td>
<td>11 (12.9)</td>
<td>9 (10.6)</td>
<td>0.634</td>
</tr>
<tr>
<td>CO exposure time (hr)</td>
<td>8.0 ± 4.3</td>
<td>8.1 ± 4.7</td>
<td>0.849</td>
</tr>
<tr>
<td>GCS score</td>
<td>9.7 ± 3.8</td>
<td>10.0 ± 3.4</td>
<td>0.549</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10 (11.8)</td>
<td>11 (12.9)</td>
<td>0.816</td>
</tr>
<tr>
<td>Hypertension</td>
<td>23 (27.1)</td>
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<td>0.612</td>
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</tr>
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<td>28 (32.9)</td>
<td>0.205</td>
</tr>
<tr>
<td>Current smoker</td>
<td>34 (40.0)</td>
<td>27 (31.8)</td>
<td>0.263</td>
</tr>
<tr>
<td>Time from rescue to ED arrival (hr)</td>
<td>3.7 ± 3.2</td>
<td>3.8 ± 3.0</td>
<td>0.815</td>
</tr>
<tr>
<td>Symptoms and sign at the ED</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss of consciousness</td>
<td>74 (87.1)</td>
<td>75 (88.2)</td>
<td>0.816</td>
</tr>
<tr>
<td>Shock</td>
<td>9 (10.6)</td>
<td>8 (9.4)</td>
<td>0.798</td>
</tr>
<tr>
<td>Seizure</td>
<td>5 (5.9)</td>
<td>5 (5.9)</td>
<td>1.000</td>
</tr>
<tr>
<td>Use of HBO_3_</td>
<td>72 (84.7)</td>
<td>75 (88.2)</td>
<td>0.501</td>
</tr>
<tr>
<td>Laboratory findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COHb (%)</td>
<td>27.3 ± 16.6</td>
<td>23.8 ± 14.6</td>
<td>0.141</td>
</tr>
<tr>
<td>Bicarbonate (mmol/L)</td>
<td>18.5 ± 4.0</td>
<td>18.7 ± 4.3</td>
<td>0.739</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>3.8 ± 3.0</td>
<td>3.9 ± 3.4</td>
<td>0.828</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.1 ± 0.5</td>
<td>1.1 ± 0.5</td>
<td>0.886</td>
</tr>
<tr>
<td>Creatinine kinase (U/L)</td>
<td>3,036.3 ± 6,094.2</td>
<td>3,648.7 ± 5,078.7</td>
<td>0.478</td>
</tr>
<tr>
<td>Troponin I (ng/mL)</td>
<td>4.4 ± 8.5</td>
<td>3.6 ± 6.1</td>
<td>0.511</td>
</tr>
<tr>
<td>Phosphate (mg/dL)</td>
<td>3.9 ± 1.7</td>
<td>3.7 ± 1.3</td>
<td>0.349</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.2 ± 0.4</td>
<td>4.2 ± 0.5</td>
<td>0.629</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>140.0 ± 3.9</td>
<td>141.0 ± 3.5</td>
<td>0.104</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.2 ± 0.6</td>
<td>4.2 ± 0.6</td>
<td>0.688</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>8.8 ± 0.6</td>
<td>8.8 ± 0.6</td>
<td>0.732</td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
<td>106.6 ± 4.8</td>
<td>107 ± 4.6</td>
<td>0.646</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number (%).


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Supplementary Figs. 1 and 2. Density plot of propensity scores according to presence of poor neurological outcome.

Funding

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**CONFLICT OF INTEREST**

No potential conflict of interest relevant to this article was reported.

**SUPPLEMENTARY MATERIALS**

Supplementary Method 1. Global Deterioration Scale.
Supplementary Table 1. Global Deterioration Scale.
Supplementary Table 2. Subgroup analysis.
Supplementary Fig. 1. Density plot of propensity scores according to the presence of poor neurological outcome.
Supplementary Fig. 2. Prognostic power for poor neurocognitive outcome by area under the receiver operator characteristic curve.

Nonrandomized study. Hidden bias may therefore be present due to the effects of unmeasured confounders. Second, although a few randomized control trials have conducted multiple neurocognitive tests (approximately six tests usually equivalent to CO screening batteries) [7,8], we only evaluated outcomes using the GDS. Our institution uses the GDS score to determine the neurocognitive prognosis of patients with CO poisoning because it assesses neurocognitive functions, such as memory and concentration, as well as activities of daily living, through interviews. We previously reported the GDS as a neurocognitive outcome in a study related to CO poisoning [30–32]. Third, continuous serum phosphate was not measured. The relationship between serum phosphate over time and poor neurologic outcome after CO poisoning was not investigated. Continuous observation of serum phosphate may reveal an unknown relationship between CO poisoning and serum phosphate level. We performed additional analysis of the interval between rescue from the CO source and sampling at the ED. However, the differences in serum phosphate between these time points and neurocognitive outcome were not statistically significant (Supplementary Table 2). Fourth, we were unable to obtain information about parathyroid hormone or serum magnesium and vitamin D levels, which could affect phosphate levels.

In conclusion, serum phosphate level evaluated at the ED did not predict poor neurocognitive outcomes 1 month after CO poisoning.
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REFERENCES

Supplementary Method 1. Global Deterioration Scale.

The Global Deterioration Scale (GDS) is a validated, reliable instrument for describing the clinical progression of dementia [1]. It is also used to determine the prognosis of patients with carbon monoxide (CO) poisoning [2–4] and those with severe chronic obstructive pulmonary disease, Alzheimer’s disease, and vasculopathy-related dementia [1,5–7].

Although the GDS score is not as diverse as a CO battery, it has the advantage of being able to recognize neurocognitive functions, such as memory and concentration, as well as activities of daily living, through interviews. Moreover, many neurocognitive function tests may be difficult for patients with sequelae. The Short-Form General Health Survey-36, a commonly used testing tool, has a set of self-reported questions; however, it is limited in evaluating patients with severe neurological impairment as it requires the ability to understand and address the questions. Digit span, trail making, and clock drawing are good evaluation tools but require short-term memory and visuospatial functions. Therefore, the GDS score can be used for all patients with CO poisoning, regardless of poisoning severity. The scale consists of 7 scores, with higher scores indicating greater severity.

REFERENCES

### Supplementary Table 1. Global Deterioration Scale

<table>
<thead>
<tr>
<th>Stage</th>
<th>Cognitive dysfunction</th>
<th>Clinical characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No cognitive decline</td>
<td><strong>Patients appear clinically normal.</strong>&lt;br&gt;No complaints of memory deficits.&lt;br&gt;No evident memory deficit on clinical interview.</td>
</tr>
<tr>
<td>2</td>
<td>Very mild cognitive decline</td>
<td><strong>Patients complain of memory deficits.</strong>&lt;br&gt;Most frequently, patients:&lt;br&gt;(a) forget where they have placed familiar objects;&lt;br&gt;(b) forget the name of someone they formerly knew well.&lt;br&gt;No objective evidence of memory deficit on clinical interview.&lt;br&gt;No objective deficits in employment or social situations.&lt;br&gt;Patients display appropriate concern about their symptoms.</td>
</tr>
<tr>
<td>3</td>
<td>Mild cognitive decline</td>
<td><strong>Earliest clear-cut deficits.</strong>&lt;br&gt;Objective evidence of memory deficit was obtained only with an intensive interview conducted by a trained geriatric psychiatrist. Concentration deficit may be evident on clinical testing.&lt;br&gt;Patients may demonstrate a reduced ability to:&lt;br&gt;(a) remember names upon introduction to new people;&lt;br&gt;(b) retain information after reading a passage from a book.&lt;br&gt;Decreased performance becomes manifest in demanding employment and social situations. Examples may include:&lt;br&gt;(a) co-workers becoming aware of the patient’s relatively poor performance;&lt;br&gt;(b) difficulties in finding words and names becoming evident to intimate acquaintances;&lt;br&gt;(c) losing or misplacing objects of value;&lt;br&gt;(d) getting lost when traveling to unfamiliar locations.&lt;br&gt;The subtlety of the clinical symptoms may be exacerbated by denial that is often manifest in these patients. Mild-to-moderate anxiety also accompanies the symptoms, typically when the patients are forced to cope with challenging employment and social demands that they find they can no longer negotiate.</td>
</tr>
<tr>
<td>4</td>
<td>Moderate cognitive decline</td>
<td><strong>Clear-cut deficits on careful clinical interview.</strong>&lt;br&gt;Deficits are manifest in many areas, such as:&lt;br&gt;(a) concentration deficit elicited in serial subtractions;&lt;br&gt;(b) decreased knowledge of current events and recent life events;&lt;br&gt;(c) upon careful questioning, patients may exhibit a deficit in memory of their personal history;&lt;br&gt;(d) decreased ability to travel alone and manage finances.&lt;br&gt;Patients can no longer perform complex tasks accurately and efficiently. However, certain abilities remain preserved, such as:&lt;br&gt;(a) orientation to time and people;&lt;br&gt;(b) familiar persons and faces can be distinguished from strangers;&lt;br&gt;(c) ability to travel to familiar locations.&lt;br&gt;Denial is often the dominant defence mechanism. The evident decline in the patients’ intellectual and cognitive capacities is too overwhelming a loss for full conscious acceptance and recognition. A flattening of effect and withdrawal from previously challenging situations are observed.</td>
</tr>
<tr>
<td>5</td>
<td>Moderately severe cognitive decline</td>
<td><strong>Patients can no longer survive without some assistance.</strong>&lt;br&gt;During interviews, patients are unable to recall a major relevant aspect of their current lives. Examples include:&lt;br&gt;(a) difficulty recalling their address or telephone number, names of close family members, such as grandchildren, or the name of the high school or university from which they graduated;&lt;br&gt;(b) some disorientation to time (date, day of the week, season) or location;&lt;br&gt;(c) well-educated patients may have difficulty counting backwards from 40 by 4s or from 20 by 2s.&lt;br&gt;Patients retain the knowledge of many major facts regarding themselves and others. They invariably know their own names and generally know their spouse and children’s names. They require no assistance with toileting and eating but may have some difficulty choosing the proper clothing to wear and may occasionally clothe themselves improperly (e.g., put their shoes on the wrong feet).</td>
</tr>
<tr>
<td>6</td>
<td>Severe cognitive decline</td>
<td><strong>Patients may occasionally forget the name of their spouse, on whom they depend entirely for survival.</strong>&lt;br&gt;Patients are largely unaware of all recent events and experiences in their lives.</td>
</tr>
</tbody>
</table>

(Continued on the next page)
### Supplementary Table 1. (Continued)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Cognitive dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Very severe cognitive decline</td>
</tr>
<tr>
<td></td>
<td><strong>All verbal abilities are lost.</strong></td>
</tr>
<tr>
<td></td>
<td>Frequently there is no speech at all, and only grunting remains.</td>
</tr>
<tr>
<td></td>
<td>Patients have urinary incontinence and require assistance with toileting and eating.</td>
</tr>
<tr>
<td></td>
<td>They lose psychomotor skills (e.g., the ability to walk). The brain appears no longer</td>
</tr>
<tr>
<td></td>
<td>able to tell the body what to do. Generalized cortical and focal neurologic signs and</td>
</tr>
<tr>
<td></td>
<td>symptoms are frequently present.</td>
</tr>
</tbody>
</table>

They retain some knowledge of their past, but this knowledge is very uncertain. They are generally unaware of their surroundings, the year, or the season and may have difficulty counting backward, and sometimes forward, from 10. Patients require substantial assistance with activities of daily living. These are quite variable and include:

(a) delusional behavior (e.g., patients may accuse their spouse of being an impostor, may talk to imaginary figures in the environment, or their own reflection in the mirror);

(b) obsessive symptoms (e.g., continual repetition of simple cleaning activities);

(c) anxiety symptoms, agitation, and previously non-existent violent behavior;

(d) cognitive abulia (i.e., loss of willpower because they cannot carry a thought long enough to determine a purposeful course of action).
**Supplementary Table 2.** Subgroup analysis

<table>
<thead>
<tr>
<th>Time from rescue to ED arrival (hr)</th>
<th>Phosphate (mg/dL)</th>
<th>Favorable</th>
<th>Poor outcome</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 3.05 (n = 86)</td>
<td>4.1 ± 1.9</td>
<td>3.9 ± 1.7</td>
<td>0.750</td>
<td></td>
</tr>
<tr>
<td>&lt; 3.05 (n = 84)</td>
<td>3.8 ± 1.4</td>
<td>3.5 ± 0.8</td>
<td>0.348</td>
<td></td>
</tr>
</tbody>
</table>

ED, emergency department.
Supplementary Fig. 1. Density plot of propensity scores according to presence of poor neurological outcome. (A) Before and (B) after propensity score matching.
Supplementary Fig. 2. Prognostic power for poor neurocognitive outcome by area under the receiver operator characteristic curve.
Impact of COVID-19 outbreak on acute gallbladder disease in the emergency department

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Objective Acute gallbladder disease (AGD) is frequent in the emergency department (ED) and usually requires emergency surgery. However, only a few studies have reported the impact of COVID-19 on AGD. The goal of this study was to evaluate the time between symptom onset and surgery and the perioperative severity of AGD during the COVID-19 pandemic compared to before the era of COVID-19.

Methods This retrospective, single-center cohort study included patients who presented to the ED with suspected AGD and who underwent emergency cholecystectomy. We designed a before-after comparative study, and the intervention was the COVID-19 outbreak. The 6-month period after the COVID-19 outbreak was defined as the post-COVID group, whereas the pre-COVID group consisted of the same period in the previous year. The primary outcome was the time from symptoms to surgery. We evaluated the time intervals between symptom onset and ED arrival and between ED arrival and surgery. The secondary outcomes were preoperative and postoperative severity indexes.

Results A total of 316 patients was analyzed. The post-COVID group showed longer duration from symptom onset to ED arrival (34.0 hours vs. 15.0 hours, P < 0.001) and longer time interval from ED arrival to surgery (16.2 hours vs. 10.2 hours, P < 0.001) than the pre-COVID group. The overall time interval between symptom onset to surgery was longer in the post-COVID group than the pre-COVID group (71.5 hours vs. 33.5 hours, P < 0.001). The post-COVID group showed higher preoperative Simplified Acute Physiology Score II scores than the pre-COVID group (20.1 vs. 18.2, P = 0.045). The proportion of moderate or severe disease increased in the post-COVID group (78% vs. 65%, P = 0.017). The durations of hospital stay (7.0 days vs. 5.0 days, P < 0.001) and intensive care unit stay (27.1 hours vs. 10.8 hours, P = 0.008) were longer in the post-COVID group than in the pre-COVID group.

Conclusion During the pandemic, the time interval between symptom onset to surgery was significantly increased among patients with AGD. Concomitantly, higher preoperative severity indexes and longer hospital stay were reported with a delay in emergency surgery.

Keywords Acute cholecystitis; COVID-19; Pandemics; Cholecystectomy
INTRODUCTION

Acute gallbladder disease (AGD) is a common clinical issue among patients who visit the emergency department (ED). Acute cholecystitis (AC) with gallstones is the most frequent presentation of AGD and can manifest as inflammation without gallstones or colic pain without inflammation [1]. The diagnosis and management plans for this disease are well established [2–4]. Early laparoscopic cholecystectomy (LC) is recommended in AC, and percutaneous drainage of the gallbladder or medical treatment offers alternative options [5]. Delay in proper management may lead to unfavorable outcomes for patients with AGD.

The unexpected spread of novel coronavirus infection has significantly affected healthcare worldwide. After the COVID-19 outbreak, global ED visits drastically decreased and did not return to the level before the pandemic for more than 6 months [6–12]. Furthermore, the number of ED visits with critical and emergent illnesses concomitantly decreased [9,12]. Deferring necessary care and avoiding visiting healthcare facilities were reported as potential causes of these decreases [11–13].

Several studies have reported the impact of COVID-19 on AGD worldwide. According to the position statement by the World Society of Emergency Surgery, LC remains the treatment of choice for AC in the era of COVID-19 [14]. Furthermore, LC is indicated in COVID-19–positive patients for which medical treatment or interventional management is ineffective [15]. A study has reported the challenges and dilemmas in AC management during the COVID–19 pandemic in Singapore; however, the study was limited to opinions of surgeons by survey without clinical outcomes [16]. Studies from the United States and Ireland have shown a reduced number of AC cases during the pandemic and have discussed the severity of the disease [17,18]. Thus, we designed a study to investigate the impact of COVID–19 on patients with AGD who visited an emergency room (ER) and underwent emergency cholecystectomy in Korea. The goal of this study was to evaluate the time between symptom onset and surgery and the perioperative severity of AGD during the COVID–19 pandemic compared to before the era of COVID–19. We analyzed the integrated clinical aspects of particular gallbladder diseases under pandemic situations from an Asian perspective because Asia was the region of origin for the novel coronavirus outbreak.

METHODS

We designed a before and after comparative study on patients with AGD undergoing emergency cholecystectomy. The retrospective cohort study was conducted at an academic teaching hospital (CHA University Gumi Medical Center, Gumi, Korea). This secondary referral center is a level 1 regional ED in Korea, and the annual number of emergency cholecystectomies at the institution ranges from 300 to 350 [19]. Patients who were managed during the 6-month period after the COVID–19 outbreak from March 1 to August 31, 2020, were defined as the post-COVID group, whereas the pre-COVID group consisted of patients who were managed during the same period in the previous year from March 1 to August 31, 2019. The study was approved by the Institutional Ethics Review Board of CHA Gumi Medical Center (No. GM21-04), and individual consent for this retrospective analysis was waived.

We collected data from the medical records of patients who visited the ED with a clinical presentation of AGD and those who were suspected to have AGD upon ED evaluation. We defined AGD as follows: (1) clinical manifestation such as right upper quadrant or upper abdominal colic pain and history of fever or (2) acute inflammation of the gallbladder, presence of gallstones, or other abnormal findings of the gallbladder on ultrasonography or computed tomography (CT). The attending emergency physician and the senior hepatopancreatobiliary surgeon made the decision...
Impact of COVID-19 on AGD in the ED

Regarding surgery. We excluded patients with incomplete data, those who refused to undergo surgery, and those who were managed by percutaneous drainage first and underwent delayed cholecystectomy afterward.

Demographic and clinical data were age, sex, vital signs and mental status upon ED arrival, severity of pain, and duration of symptoms before ED arrival. Moreover, we obtained the results of preoperative laboratory and radiological evaluations at the ED, the interval between ED arrival and surgery, duration of surgery, the results of pathological evaluations, total duration of hospital stay after surgery, duration of intensive care unit (ICU) stay, the occurrence of readmission within 30 days after discharge, and in-hospital mortality.

We measured the severity of pain using a numerical rating scale, which is a simple popular tool in the ED [20]. Individual patients rated their pain from 0 to 10 upon ED arrival, with a score of 0 indicating “absolutely no pain” and a score of 10 representing “the worst imaginable pain.” To estimate the disease severity of each patient, the Simplified Acute Physiology Score (SAPS) II, Acute Physiology and Chronic Health Evaluation (APACHE) II, and quick Sepsis-related Organ Failure Assessment (qSOFA) were used. The qSOFA score was rated positive when two or three criteria were fulfilled. Preoperative diagnosis and severity grading of AC were determined according to the Tokyo Guidelines 2018 (TG18) [2]. All the severity factors were measured and calculated based on clinical information and preoperative evaluation at the ED, except urine output, which was measured for 8 hours after ED arrival throughout the hospital stay. The pathologist confirmed the final diagnosis after cholecystectomy.

We presented categorical variables as frequencies and percentages, whereas continuous variables were reported as means ± standard deviations or medians with interquartile ranges. The normality of the data was evaluated using skewness and kurtosis analyses and the Shapiro-Wilk test. The chi-square test or Fisher exact test was used to compare categorical variables. A t-test was used to compare normally distributed continuous variables, and non-
normally distributed data were evaluated using the Mann–Whitney U-test. All tests were two-tailed, and P-values less than 0.05 were used to indicate statistical significance. Data were analyzed using the IBM SPSS ver. 27 (IBM Corp).

The primary outcome of interest was the time from symptom onset to surgery. We evaluated the time intervals between symptom onset and ED arrival and between ED arrival and surgery. The secondary outcome was the perioperative severity index. We compared postoperative factors of length of in-hospital stay, total accumulated duration of ICU stay, in-hospital mortality, and results of the pathological examinations between the groups.

RESULTS

General description
In total, 358 patients presented to the ED with suspicion of AGD during the previously mentioned periods. After excluding 42 patients according to the exclusion criteria, 316 who underwent emergency cholecystectomy for AGD were included for analysis (Fig. 1). Demographic and preoperative clinical data are summarized in Table 1. No significant differences in age and sex were observed between groups (P = 0.355 and P = 0.196, respectively).

Primary outcomes
The duration of symptoms before ED arrival was significantly longer in the post-COVID group than in the pre-COVID group (34.0 hours [range, 9.0–98.5] vs. 15.0 hours [range, 5.0–66.0], P < 0.001) (Fig. 2). The post-COVID group showed a significantly longer time interval between ED arrival and surgery than the pre-COVID group (16.2 hours [range, 7.7–43.2] vs. 10.2 hours [range, 6.3–19.5], P = 0.008, respectively). Although the number of patients admitted to the ICU, those who were readmitted within 30 days after discharge, and in-hospital mortality was not significantly different between the two groups.

Up to 90% of the patients had AC on the pathological evaluation, and acute calculus cholecystitis was the most common clinical condition in both groups (64.4% and 63.5%, respectively). The post-COVID group had a trend of a higher proportion of complicated AC (such as acute suppurative cholecystitis or acute gangrenous cholecystitis) than the pre-COVID group (23.5% vs. 20.4%, P = 0.501) (Table 2). In addition to AC, chronic calculus cholecystitis, cholelithiasis without inflammation, and gallbladder malignancy were reported.

Secondary outcomes
On analysis of clinical severity estimation, the post-COVID group showed higher SAPS II and APACHE II scores than the pre-COVID group. However, only differences in SAPS II scores were statistically significant (20.1 ± 8.9 vs. 18.2 ± 7.7, P = 0.045) (Table 2). Severity grading using the TG18 criteria showed relevant differences between the groups. The proportion of patients with moderate or severe disease (TG18 grade II or III) significantly increased in the post-COVID group relative to the pre-COVID group (52.3% vs. 38.9%, P = 0.017).

The mean operation time was not statistically different between the two groups (P = 0.414). The total duration of hospital stay and the mean duration of ICU stay were longer in the post-COVID group than in the pre-COVID group with significant differences (7 days [range, 5–10] vs. 5 days [range, 4–7], P < 0.001; 27.1 ± 69.2

DISCUSSION

In this study, we found that the COVID-19 pandemic negatively affected particular surgical emergencies associated with AGD. The overall time interval between symptom onset to surgery was

Table 1. Demographic characteristics and preoperative clinical summary of the study participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pre-COVID group¹</th>
<th>Post-COVID group²</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>59 (50–75)</td>
<td>59 (49–71)</td>
<td>0.355</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>82 (49.1)</td>
<td>84 (56.4)</td>
<td>0.196</td>
</tr>
<tr>
<td>Female</td>
<td>85 (50.9)</td>
<td>65 (43.6)</td>
<td></td>
</tr>
<tr>
<td>Clinical presentation at ED arrival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital sign</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>96.8 ± 17.2</td>
<td>95.4 ± 15.7</td>
<td>0.460</td>
</tr>
<tr>
<td>Pulse rate (beats/min)</td>
<td>84.5 ± 15.9</td>
<td>82.9 ± 14.6</td>
<td>0.351</td>
</tr>
<tr>
<td>Body temperature (°C)</td>
<td>37.0 ± 0.8</td>
<td>37.1 ± 0.9</td>
<td>0.219</td>
</tr>
<tr>
<td>SpO₂ (%)</td>
<td>98.6 ± 0.8</td>
<td>98.6 ± 1.2</td>
<td>0.963</td>
</tr>
<tr>
<td>Pain severity (numeric rating scale score)</td>
<td>3.6 ± 1.3</td>
<td>3.7 ± 1.8</td>
<td>0.377</td>
</tr>
<tr>
<td>Preoperative data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cell count (L/mm³)</td>
<td>11,069 ± 4,275</td>
<td>10,970 ± 4,280</td>
<td>0.836</td>
</tr>
<tr>
<td>Segmented neutrophils (%)</td>
<td>75.5 ± 11.5</td>
<td>74.6 ± 17.0</td>
<td>0.569</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.1 ± 0.9</td>
<td>0.9 ± 0.4</td>
<td>0.079</td>
</tr>
<tr>
<td>Serum bilirubin (mg/dL)</td>
<td>1.3 ± 1.3</td>
<td>1.4 ± 1.5</td>
<td>0.723</td>
</tr>
<tr>
<td>C-reactive protein (mg/dL)</td>
<td>6.1 ± 7.8</td>
<td>5.6 ± 6.9</td>
<td>0.556</td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range), number (%), or mean ± standard deviation.

¹Patients who were managed during the 6-month period before the COVID-19 outbreak, from March 1 to August 31, 2019. ²Patients who were managed during the 6-month period after the COVID-19 outbreak, from March 1 to August 31, 2020. ³Laboratory study.
Table 2. Primary and secondary outcomes of the study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-COVID group(^a) (n = 167)</th>
<th>Post-COVID group(^b) (n = 149)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time from symptom to surgery (hr)</td>
<td>33.5 (19.3–79.1)</td>
<td>71.5 (25.5–140.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Time from symptom to ED arrival (hr)</td>
<td>15.0 (5.0–66.0)</td>
<td>34.0 (9.0–98.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Time from ED arrival to surgery (hr)</td>
<td>10.2 (6.3–19.5)</td>
<td>16.2 (7.7–43.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Secondary outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity estimation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAPS II score</td>
<td>18.2 ± 7.7</td>
<td>20.1 ± 8.9</td>
<td>0.045</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>5.5 ± 3.2</td>
<td>5.7 ± 4.0</td>
<td>0.651</td>
</tr>
<tr>
<td>Positive qSOFA</td>
<td>6 (3.6)</td>
<td>6 (4.0)</td>
<td>0.840</td>
</tr>
<tr>
<td>Tokyo Guidelines (grade)</td>
<td></td>
<td></td>
<td>0.017</td>
</tr>
<tr>
<td>I (mild)</td>
<td>102 (61.1)</td>
<td>71 (47.7)</td>
<td></td>
</tr>
<tr>
<td>II (moderate)</td>
<td>57 (34.1)</td>
<td>70 (47.0)</td>
<td></td>
</tr>
<tr>
<td>III (severe)</td>
<td>8 (4.8)</td>
<td>8 (5.4)</td>
<td></td>
</tr>
<tr>
<td>II+III</td>
<td>65 (38.9)</td>
<td>78 (52.3)</td>
<td></td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>48 (38–60)</td>
<td>46 (38–70)</td>
<td>0.414</td>
</tr>
<tr>
<td>Length of hospital stay (day)</td>
<td>5 (4–7)</td>
<td>7 (5–10)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Intensive care unit care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of stay (hr)</td>
<td>10.8 ± 36.6</td>
<td>27.1 ± 69.2</td>
<td>0.008</td>
</tr>
<tr>
<td>No. of patients</td>
<td>16 (9.6)</td>
<td>19 (12.8)</td>
<td>0.370</td>
</tr>
<tr>
<td>Readmission within 30 days</td>
<td>6 (3.6)</td>
<td>9 (6.0)</td>
<td>0.307</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>1 (0.6)</td>
<td>2 (1.3)</td>
<td>0.496</td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range), mean ± standard deviation, or number (%).

ED, emergency department; SAPS, Simplified Acute Physiology Score; APACHE, Acute Physiology and Chronic Health Evaluation; qSOFA, quick Sepsis-related Organ Failure Assessment.

\(^a\)Patients who were managed during the 6-month period before the COVID-19 outbreak, from March 1 to August 31, 2019. \(^b\)Patients who were managed during the 6-month period after the COVID-19 outbreak, from March 1 to August 31, 2020.
COVID-19-protected requires more time. As a result, several inev-
ensure surgical team safety, organizing an operating room to be
be performed in patients who underwent abdominal CT [26]. To
for all emergency surgical patients [25]. Additional chest CT should
were added at the ED. The World Society of Emergency Surgery
VID-19 pandemic [23,24]. Various mandatory preoperative steps
set and ED arrival is associated with a better prognosis in numer-
prolonged operative time in the post-COVID group [27].
Although 2 years have passed since the original outbreak, we
have not entirely overcome the global crisis. Furthermore, we are
threatened by potential dangers, such as novel viral variants. As
outlined in this study, the pandemic has critically affected the
system of emergency medicine, as well as the particular urgent
surgical entity. Future strategies should be discussed to minimize
the risk of COVID transmission. A rapid transition to COVID-19-
specific EDs can be a proactive solution to the limited emergency
care resources during a pandemic is another considerable factor. One regional study re-
ported shortage of emergency medical services and subsequent delays in transport of patients with severe illnesses [23].

Longer ED stays have been reported worldwide during the CO-
VID-19 pandemic [23,24]. Various mandatory preoperative steps
were added at the ED. The World Society of Emergency Surgery
recommended performing tests for COVID-19 infection at the ED
for all emergency surgical patients [25]. Additional chest CT should
be performed in patients who underwent abdominal CT [26]. To
ensure surgical team safety, organizing an operating room to be
COVID-19-protected requires more time. As a result, several inev-
Table 3. Final pathological diagnoses of patients with acute gallbladder
disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-COVID group$^a$ (n = 167)</th>
<th>Post-COVID group$^b$ (n = 149)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-AC</td>
<td>22 (13.2)</td>
<td>15 (10.1)</td>
<td>0.391</td>
</tr>
<tr>
<td>AC</td>
<td>145 (86.8)</td>
<td>134 (89.9)</td>
<td></td>
</tr>
<tr>
<td>Acute calculous cholecystitis</td>
<td>106 (63.5)</td>
<td>96 (64.4)</td>
<td>0.556</td>
</tr>
<tr>
<td>Acute acalculous cholecystitis</td>
<td>5 (3.0)</td>
<td>3 (2.0)</td>
<td>0.580</td>
</tr>
<tr>
<td>Acute suppurative cholecystitis</td>
<td>20 (12.0)</td>
<td>23 (15.4)</td>
<td>0.371</td>
</tr>
<tr>
<td>Acute gangrenous cholecystitis</td>
<td>14 (8.4)</td>
<td>12 (8.1)</td>
<td>0.951</td>
</tr>
<tr>
<td>Complicated AC$^c$</td>
<td>34 (20.4)</td>
<td>35 (23.5)</td>
<td>0.501</td>
</tr>
</tbody>
</table>

Values are presented as number (%).

$^a$Patients who were managed during the 6-month period before the COVID-19 outbreak, from March 1 to August 31, 2019. $^b$Patients who were managed during the 6-month period after the COVID-19 outbreak, from March 1 to August 31, 2020. $^c$Acute suppurative cholecystitis + acute gangrenous cholecystis.

longer during the pandemic. In addition, the duration of symp-
toms before ED arrival was significantly prolonged, and there was
a remarkable delay in emergency surgery. Secondarily, several peri-
operative indexes including severity scores and grading and length
of hospital stay were poor during the pandemic.

Needless to say, a shorter time interval between symptom on-
set and ED arrival is associated with a better prognosis in numer-
os critical disease entities, such as acute coronary syndrome and
cerebrovascular accidents [13]. Similarly, prolonged complaint
duration is a major component of severity grading using the TG18
in AC. One study has suggested a relationship between longer
symptom duration and surgical outcomes of AGD during the CO-
VID-19 pandemic [21]. We postulate that delayed ED presenta-
tions of the post-COVID group were causally related to the higher
TG grades and poorer severity scores in this study. The public ten-
dency to postpone emergency care or the shutdown of EDs, which
were discussed as factors for the decline in the number of ED vis-
its, potentially affected these trends of delay [8,12,22]. Further-
more, the limited prehospital emergency care resources during a
pandemic is another considerable factor. One regional study re-
ported shortage of emergency medical services and subsequent delays in transport of patients with severe illnesses [23].

Longer ED stays have been reported worldwide during the CO-
VID-19 pandemic [23,24]. Various mandatory preoperative steps
were added at the ED. The World Society of Emergency Surgery
recommended performing tests for COVID-19 infection at the ED
for all emergency surgical patients [25]. Additional chest CT should
be performed in patients who underwent abdominal CT [26]. To
ensure surgical team safety, organizing an operating room to be
COVID-19-protected requires more time. As a result, several inev-
itable delays occurred before surgery in this study. The guidelines
recommend that early LC be performed as soon as possible to achi-
eve better outcomes in AC [4]. In this study, we observed poor clinical effects, such as lengthened total duration of hospital and
ICU stays in the post-COVID group. Furthermore, a larger propor-
tion of complicated AC was possibly associated with those periods
between the groups. Consequently, the prolonged interval between
ER arrival and surgery, in conjunction with delayed ED presenta-
tion, may have contributed to worse surgical outcomes.

The operative duration should be considered in the era of CO-
VID-19, although no statistical significance was observed in this
study. Surgical smoke, which contains toxic components, is fre-
cently produced during abdominal surgery. Still, there is no clear
evidence to indicate the presence of severe acute respiratory syn-
drome coronavirus 2 in surgical smoke; in contrast, viral RNA has
been detected in peritoneal fluid [14]. However, a considerable
risk of infection remains for the surgical team, especially during
laparoscopic surgery. The guidelines recommend equipping the
necessary personal protective equipment for the surgical staff
[25]. Using ultra-low particulate air filters in the operating room
may be effective [14]. Proper protocols for the entire operative
management should be established to perform a safe surgical
procedure [25]. To ensure the specific safety precautions, a longer
operative duration is necessary before the end of the COVID-19
pandemic. Substantially longer operative duration is associated
with a higher risk of complications, and we should consider the
potential negative effect of prolonged operative time in the post-
COVID group [27].

Although 2 years have passed since the original outbreak, we
have not entirely overcome the global crisis. Furthermore, we are
threatened by potential dangers, such as novel viral variants. As
outlined in this study, the pandemic has critically affected the
system of emergency medicine, as well as the particular urgent
surgical entity. Future strategies should be discussed to minimize
the risk of COVID transmission. A rapid transition to COVID-19-
specific EDs can be a proactive solution to the limited emergency
care resources [28]. Against the fear of hospital-acquired infec-
tion of the public, ED staff should exert necessary efforts to as-
sure safety with pertinent preventive protocols [7]. Regardless of
the specific conditions, appropriate emergency care is key for
global health.

This study has obvious limitations. First, the retrospective study
design is limited in helping us understand the current situations.
A mixed-methods study will be needed, including a survey on pa-
tient health care use like avoidance or hesitancy to seek care. A
prospective design should be considered in future studies. Sec-
ond, collected from a single institution, the data may not repre-
sent the entire nation. Thus, the results should be interpreted cautiously. The duration of symptoms varied by patient. As time passed for days or weeks after the onset, it became difficult to remember and express the exact time. The low accuracy of particular time factors could be an additional limitation. Other limitations included the absence of COVID-19-positive patients in this study. As the institution has been designated to care for COVID-19-positive patients since 2021, we could not conduct an integrated analysis between COVID-19 and AGD.

In conclusion, during the pandemic, the time interval between symptom onset to surgery was significantly increased among patients with AGD. Concomitantly, poor preoperative severity indexes and longer hospital stay were reported with a sequential delay in emergency surgery.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

FUNDING

None.

AUTHOR CONTRIBUTIONS

Conceptualization: DS, WYN; Data curation: MSPC, CWP; Validation: WYN; Writing–original draft: DS; Writing–review & editing: all authors.

All authors read and approved the final manuscript.

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Dal Sakong, et al.

The impact of the COVID–19 pandemic on in–hospital mortality in patients admitted through the emergency department

Changgyun Kim, Juncheol Lee, Yongil Cho, Jaehoon Oh, Hyunggoo Kang, Tae Ho Lim, Byuk Sung Ko
Department of Emergency Medicine, Hanyang University College of Medicine, Seoul, Korea

Objective The COVID–19 pandemic might have adversely affected outcomes of patients in emergency departments (EDs). The aim of this study is to evaluate the impact of the COVID–19 pandemic on in patients admitted through the emergency department.

Methods This study is a single-center, retrospective, observational cohort study. We compared the prognosis of patients admitted through the ED before the COVID–19 pandemic (November 2018 to June 2019) and after COVID–19 (November 2020 to June 2021). The primary outcome was in–hospital mortality. Multivariable logistic regression analysis was performed to determine whether the COVID–19 pandemic was independently associated with patient prognosis.

Results The number of patients admitted through the ED before and after COVID–19 was 5,333 and 4,625, respectively. The mean ED length of stay before and after COVID–19 was 401 and 442 minutes, respectively (P < 0.001). The number of in–hospital deaths before and after COVID–19 were 269 (5.0%) and 322 (7.0%), respectively (P < 0.001). Multivariable logistic regression analysis showed that the COVID–19 period was significantly associated with higher in–hospital mortality (adjusted odds ratio, 1.37; 95% confidence interval, 1.12–1.67; P = 0.002).

Conclusion In the COVID–19 period, in–hospital mortality increased compared to that before COVID–19 among hospitalized ED patients.

Keywords Hospital emergency service; COVID–19; Mortality
INTRODUCTION

The COVID-19 pandemic brought many changes to the medical environment and processes of emergency departments (EDs). The total number of patients visiting the ED decreased significantly during the COVID-19 period, although the proportion of admitted patients increased in one study [1]. The COVID-19 pandemic increased the number of people leaving emergency rooms without being seen [2,3]. One study found that ED length of stay (LOS) was significantly longer during the COVID-19 period than before, despite a smaller volume of patients in the COVID-19 period [4]. The time to provide medical care to patients was delayed due to concerns about the spread of COVID-19 in hospitals [5]. Admission to most Korean hospitals was allowed only after confirming negative COVID-19 polymerase chain reaction (PCR) results and isolating accordingly. In one study, PCR-based testing on admission was an effective component of COVID-19 diagnosis and reduced risk of in-hospital transmission [6]. During the pandemic, there were many efforts to decrease the time to a COVID-19 test result [7,8]. Nevertheless, the ED LOS for patients admitted through the ED continued to increase [4].

A number of studies have shown that the longer the LOS in the ED, the worse the patient's outcome, because longer ED LOS often involves delay of timely and appropriate interventions, which increases condition severity and risk for poor outcomes [9–13]. Such treatment delays might have contributed to the development of time-dependent complications and subsequently higher intensive care unit (ICU) or general ward (GW) mortality [14]. For situations requiring urgent treatment, admission delays may worsen patient prognosis [15,16].

We hypothesized that COVID-19 had negative effects on patient prognosis. The purpose of this study was to determine whether there was a difference in in-hospital mortality among patients admitted through the ED before and after the COVID-19 pandemic.

METHODS

Ethical statements

The Institutional Review Board of Hanyang University Seoul Hospital of Korea approved the study (No. 2021-09-018). The requirement for informed consent was waived due to the observational nature of this study.

Study design and population

This is a retrospective observational cohort study conducted from November 2018 to June 2019 and from November 2020 to June 2021. This is a before-and-after study to compare differences before and after the COVID-19 pandemic. The study included adults over 18 years of age who visited the ED of a university-affiliated hospital located in Seoul, Korea. Data from patients admitted to the GW or ICU through the ED were extracted through chart review. All patients in the COVID-19 era who were admitted through the ED underwent COVID-19 PCR testing and were isolated accordingly. When COVID-19-related symptoms or epidemiological suspicions were observed and hospitalization was judged to be necessary, a routine PCR test or rapid molecular test (Xpert Xpress SARS-CoV-2, Cepheid) was performed. Results were obtained after 8 or 2 hours for routine PCR and rapid PCR, respectively. Exclusion criteria were direct transfer to another hospital from the ED, invalid admission code data, and do-not-resuscitate (DNR) orders.

Definitions and outcomes

The time-before-COVID-19 group included patients admitted to the GW or ICU through the ED of our hospital between November 2018 to June 2019. The after-COVID-19 group included patients admitted to the GW or ICU through the ED between November 2020 to June 2021. From November 2020, COVID-19 PCR was performed on all patients admitted to the GW or ICU through the ED. Only when the PCR test was negative was a patient admitted to the GW or ICU. PCR-positive patients were admitted to the COVID-19 isolation ward. The primary outcome of the study was in-hospital mortality. Secondary outcomes were ED LOS, use of mechanical ventilation, vasopressor use, continuous renal replacement therapy (CRRT), and ICU admission.

Statistical analysis

The study data are reported as mean ± standard deviation or median with interquartile range for continuous variables as appropriate. Student t-test or the Mann-Whitney U-test was used to compare continuous variables. The chi-square test and Fisher exact test were used to compare categorical variables, the results of which are reported as absolute or relative frequency. A logistic regression model was used to assess the independent association of after COVID-19 period on in-hospital mortality, with multivariable adjustment for confounding variables that were significant in univariable analyses. Variables yielding P-values < 0.1 in univariable analysis were entered into a backward multivariable logistic regression analysis. A P-value of < 0.05 was considered significant. All statistical analyses were performed using SPSS ver. 18 (SPSS Inc).
RESULTS

Participant characteristics
A total of 5,455 patients was screened by chart review from November 2018 to June 2019. Of these, 49 patients with invalid admission code data, 22 patients who were directly transferred from the ED to another hospital, and 51 patients with DNR orders were excluded. Finally, 5,333 patients were included in the before-COVID-19 group. Of the 4,761 patients who were screened by chart review from November 2020 to June 2021, 77 with invalid data, 19 directly transferred from the ED to another hospital, and 40 with DNRs were excluded. Finally, 4,625 patients were included in the after-COVID-19 group (Fig. 1).

The mean age of patients in the before-COVID-19 and after-COVID-19 groups was 60.2 and 62.6 years, respectively (Table 1). The mean ED LOS in the after-COVID-19 group was significantly longer than in the before-COVID-19 group (442 minutes vs. 401 minutes, P < 0.001). The number of patients who received mechanical ventilation was 355 (6.7%) before COVID-19 and 195 (4.2%) after COVID-19 (P < 0.001). In-hospital mortality before and after COVID-19 was 269 (5.0%) and 322 (7.0%), respectively (P < 0.001). The other baseline characteristics of the study population are summarized in Table 1. During the COVID-19 period, there were 65 COVID-19 cases (1.4% of all cases), of whom 14 died (4.3% of all deaths). There were 2,284 (42.8%) and 2,238 patients (48.4%) admitted to internal medicine before and after COVID-19, respectively (Supplementary Table 1). The number of patients admitted to general surgery before and after COVID-19 was 425% and 433%, respectively.

Multivariable logistic regression analysis to predict outcomes
To examine the effect of the COVID-19 pandemic on patient in-hospital mortality, multivariable logistic regression was performed (Tables 2, 3). The COVID-19 pandemic was significantly associated with higher in-hospital mortality (adjusted odds ratio [aOR], 1.37; 95% confidence interval [CI], 1.12–1.67; P = 0.002). Old age, heart rate, total bilirubin, creatinine, and lactate level were also independently associated with higher in-hospital mortality (aOR, 1.03, 1.01, 1.06, 1.08, and 1.14, respectively), as were systolic blood pressure and albumin (aOR, 0.99 and 0.35, respectively; both P < 0.001). Additionally, we performed multivariable logistic regression analysis for factors predicting secondary outcomes. The COVID-19 pandemic was significantly associated with lower mechanical ventilator application, vasopressor use, and CRRT application (aOR, 0.45, 0.77, and 0.71, respectively; P < 0.001, P = 0.002, and P = 0.031, respectively) (Supplementary Tables 2–4). However, the COVID-19 pandemic was not associated with increased ICU admission (aOR, 0.86; 95% CI, 0.74–1.01; P = 0.06) (Supplementary Table 5).

Subgroup analysis
Patients transferred from external hospitals were excluded, and only patients who directly visited the ED were analyzed. In-hospital mortality in the after-COVID-19 group was significantly higher than in the before-COVID-19 group (6.7% vs. 4.5%, P < 0.001) (Table 4). ED LOS of the direct ED-visited group was 413 ± 423 minutes before COVID-19 and 467 ± 406 minutes after COVID-19 (P < 0.001). Significantly more patients presenting directly to our ED were treated with mechanical ventilation in the before-COVID-19 patient group than in the after-COVID-19 patient group (6.1% vs. 3.3%, P < 0.001).

Fig. 1. Flow chart of study participants. ICU, intensive care unit; ED, emergency department; DNR, do not resuscitate.
We also compared outcomes of patients admitted to the ICU. Before COVID-19, 1,203 patients were admitted to the ICU from the ED; this number was 1,047 patients after COVID-19 (Table 5). The mean ED LOS was 425 ± 451 minutes before COVID-19 and 451 ± 460 minutes after COVID-19 (P = 0.201). Mechanical ventilation was used significantly more often before COVID-19 than after (28.3% vs. 16.5%, P < 0.001). In-hospital deaths before and after COVID-19 were 187 (15.5%) and 188 (18.0%), respectively (P = 0.14).

### DISCUSSION

After adjusting for confounding variables, in-hospital mortality of patients admitted through the ED in the after-COVID-19 period was significantly higher than before the COVID-19 period. Although we could not compare severity between the two groups, there were no differences in the proportion of vasopressor or CRRT use before and after COVID-19. Rather, the proportion of...
patients receiving mechanical ventilation was significantly lower after COVID-19 than before, although in-hospital mortality was higher. The number of patients admitted to the ICU from the ED did not differ significantly before and after COVID-19.

We investigated changes between the before-COVID-19 and after-COVID-19 periods for ED LOS and prognosis of patients admitted through the ED. Several studies have reported an association between ED LOS and patient prognosis. Furthermore, associations between COVID-19 and ED LOS have been reported [1, 4–19]. The sample size of this study is relatively large. Another strength of our study is that the treatment protocol was consistent for all patients given the single-center study design. Although severity could not be directly compared between the time points, the variables that could affect patient prognosis did not show a statistical difference between the two periods, and some variables with a difference did not appear to have a clinical effect.

There are several possible explanations for a patient’s poor prognosis during the after-COVID-19 period. Since the spread of COVID-19, more people are staying at home to maintain social distance. Meanwhile, the numbers of remote treatments and postponed scheduled treatments are increasing [20]. In addition to the shift toward remote treatment, COVID-19 has also impacted hospital admissions and visits unrelated to COVID-19 itself [21]. Studies in Spain and Italy have shown a reduction in hospitalizations and procedures related to myocardial infarction and acute coronary syndrome [22, 23]. Thus, it is possible that these patient did not receive timely treatment before their conditions worsened, and the severity was already high when patients arrived at the ED. In addition, as shown in an out-of-hospital cardiac arrest study, the longer the prehospital transport time, the worse the patient’s treatment outcome [24]. In patients who visited the ED for other conditions, the delay in prehospital transport due to lack of isolation rooms might be the cause of increased in-hospital mortality. However, our data do not have information about prehospital transport time and cannot be verified. Changes in the

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Before COVID-19 (n = 3,260)</th>
<th>After COVID-19 (n = 3,285)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency department stay (min)</td>
<td>413 ± 423</td>
<td>467 ± 406</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>147 (4.5)</td>
<td>220 (6.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>198 (6.1)</td>
<td>107 (3.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Norepinephrine use</td>
<td>249 (7.6)</td>
<td>281 (8.6)</td>
<td>0.189</td>
</tr>
<tr>
<td>Intensive care unit admission</td>
<td>554 (17.0)</td>
<td>665 (20.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Continuous renal replacement therapy</td>
<td>77 (2.4)</td>
<td>82 (2.5)</td>
<td>0.748</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number (%).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Before COVID-19 (n = 1,203)</th>
<th>After COVID-19 (n = 1,047)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency department stay (min)</td>
<td>425 ± 451</td>
<td>451 ± 460</td>
<td>0.201</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>187 (15.5)</td>
<td>188 (18.0)</td>
<td>0.140</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>341 (28.3)</td>
<td>173 (16.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Norepinephrine use</td>
<td>467 (38.8)</td>
<td>386 (36.9)</td>
<td>0.360</td>
</tr>
<tr>
<td>Continuous renal replacement therapy</td>
<td>162 (13.5)</td>
<td>115 (11.0)</td>
<td>0.082</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number (%).

number and proportion of patients by hospital department before and after COVID-19 may also be associated with an increase in in-hospital mortality after COVID-19. Compared with the before-COVID-19 period, the number and proportion of internal medicine and general surgery inpatients increased after the COVID-19 pandemic. However, it is difficult to conclude that the increase in the number of patients admitted to internal medicine and general surgery in the after-COVID-19 period is the cause of the increase in in-hospital mortality without adjustment for severity or diagnosis. Increased workload, lack of rest, and fear of infection or infecting others were observed in the after-COVID-19 period, especially among healthcare workers in the ED and ICU [25]. These factors might adversely affect in-hospital patient care in the after-COVID-19 period.

Several studies have shown that ED crowding and long ED LOS are associated with poor patient prognosis, hospital LOS, and cost [10]. ED crowding increases the waiting time to enter the ED, which delays the final diagnostic test or definitive treatment. In our hospital, patients had to wait in the ED until their PCR test results were confirmed, and due to a lack of isolation beds, ED crowding increased. The wait time from ED arrival to meet with medical staff also seemed to increase, leading to an increased ED LOS. Similar to another study, the number of patients who left the ED without being seen was significantly higher after COVID-19 in our hospital [3]. A main reason for leaving without being seen was the long waiting time from arrival to ED entrance. In our hospital, people arrived at the ED but were often not registered immediately if there were many waiting patients. In these instances, although not specifically calculated, it is estimated that the actual ED LOS was longer in the period after COVID-19. Frequent shifts between nurses and doctors can impede continuity of care and prioritize new patients, resulting in poor-quality care. PCR testing is essential for COVID-19 diagnosis, and as the number of confirmed COVID-19 patients in Korea increased, most Korean hospitals were admitting patients to the GW or ICU after confirming their test results [26]. One study showed that the time spent in
the ED increased after COVID-19 compared with before COVID-19 [27]. In that study, it was suggested that the cause of the increase in LOS and ED crowding was the time needed to obtain results from the COVID-19 PCR test. A study that analyzed changes in elderly patients before and after COVID-19 onset reported that the number of ED visits decreased after COVID-19, but that mortality increased, possibly due to the screening process or testing to differentiate between infected and noninfected patients [28].

This study has several limitations. First, because this is a single-center retrospective analysis, our results cannot be generalized to other medical institutions. Nevertheless, this single-center study has the advantage of a consistent treatment protocol, limiting the effect of treatment on patient outcomes. There is no international guideline stating that PCR results of all patients should be verified prior to admission from the ED to a ward or ICU. Therefore, it is not appropriate to generalize our findings regarding increased ED LOS to other medical institutions and other countries. Second, severity scores that could affect patient prognosis, such as sequential organ failure assessment score or acute physiology and chronic health evaluation scores, could not be analyzed. However, underlying disease, vital signs, and blood test results that might affect patient prognosis showed no clinically significant difference between the two groups. Moreover, proportions of vasopressor and CRRT use were not significantly different between the before-COVID-19 and after-COVID-19 periods. Considering that the frequency of mechanical ventilation has decreased since COVID-19, in-hospital mortality has not seemed to increase due to differences in severity. Finally, it cannot be concluded that an increase in ED LOS leads to an increase in in-hospital mortality. Variables that could affect a patient's in-hospital mortality were adjusted through multivariable analysis; however, it is uncertain whether the adjustment is sufficient due to the possibility of unmeasured confounders. In addition, we cannot infer causality with our findings.

In conclusion, the after-COVID-19 period was significantly associated with increased in-hospital mortality among patients hospitalized via the ED. This study suggests that the outcome of ED patients might worsen during the COVID-19 pandemic, but further research is required about what factors affected the outcome.

SUPPLEMENTARY MATERIALS

Supplementary Table 1. Comparison of the number of hospitalized patients by department before and after COVID-19
Supplementary Table 2. Multivariable logistic regression analysis of mechanical ventilator use
Supplementary Table 3. Multivariable logistic regression analysis of vasopressor use
Supplementary Table 4. Multivariable logistic regression analysis of continuous renal replacement therapy
Supplementary Table 5. Multivariable logistic regression analysis of intensive care unit admission
Supplementary materials are available at https://doi.org/10.15441/ceem.22.359.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article are reported.

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AUTHOR CONTRIBUTIONS

Conceptualization: THL, BSK; Data curation: CK, JL; Formal analysis: CK, JL; Funding acquisition: JO, HK; Investigation: JO, HK; Methodology: BSK; Project administration: BSK, CK; Resources: THL, CK; Software: THL, JO, HK; Supervision: JO, HK; Validation: JO, HK; Visualization: CK, JL, YC; Writing—original draft: CK, YC, JO, HK; Writing—review & editing: HK, THL, YC, BSK. All authors read and approved the final manuscript.

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REFERENCES

### Supplementary Table 1. Comparison of the number of hospitalized patients by department before and after COVID-19

<table>
<thead>
<tr>
<th>Department</th>
<th>Before COVID-19 (n = 5,333)</th>
<th>After COVID-19 (n = 4,625)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal medicine</td>
<td>2,284 (42.8)</td>
<td>2,238 (48.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>721 (13.5)</td>
<td>750 (16.2)</td>
<td></td>
</tr>
<tr>
<td>Pulmonology</td>
<td>432 (8.1)</td>
<td>335 (7.2)</td>
<td></td>
</tr>
<tr>
<td>Cardiology</td>
<td>367 (6.9)</td>
<td>397 (8.6)</td>
<td></td>
</tr>
<tr>
<td>Nephrology</td>
<td>368 (6.9)</td>
<td>355 (7.7)</td>
<td></td>
</tr>
<tr>
<td>Infectious diseases</td>
<td>120 (2.3)</td>
<td>191 (4.1)</td>
<td></td>
</tr>
<tr>
<td>Endocrinology</td>
<td>66 (1.2)</td>
<td>65 (1.4)</td>
<td></td>
</tr>
<tr>
<td>Hematology and oncology</td>
<td>109 (2.0)</td>
<td>91 (2.0)</td>
<td></td>
</tr>
<tr>
<td>Rheumatology</td>
<td>101 (1.9)</td>
<td>54 (1.2)</td>
<td></td>
</tr>
<tr>
<td>General surgery</td>
<td>425 (8.0)</td>
<td>433 (9.4)</td>
<td>0.014</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>500 (9.4)</td>
<td>338 (7.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Orthopedic surgery</td>
<td>459 (8.6)</td>
<td>377 (8.2)</td>
<td>0.426</td>
</tr>
<tr>
<td>Thoracic surgery</td>
<td>201 (3.8)</td>
<td>215 (4.6)</td>
<td>0.031</td>
</tr>
<tr>
<td>Urology</td>
<td>160 (3.0)</td>
<td>92 (2.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Obstetrics and gynecology</td>
<td>235 (4.4)</td>
<td>191 (4.1)</td>
<td>0.519</td>
</tr>
<tr>
<td>Ear nose and throat</td>
<td>118 (2.2)</td>
<td>37 (0.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Neurology</td>
<td>504 (9.5)</td>
<td>454 (9.8)</td>
<td>0.540</td>
</tr>
<tr>
<td>Psychiatry</td>
<td>50 (0.9)</td>
<td>49 (1.1)</td>
<td>0.545</td>
</tr>
<tr>
<td>Emergency medicine</td>
<td>332 (6.2)</td>
<td>180 (3.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Dermatology</td>
<td>11 (0.2)</td>
<td>3 (0.1)</td>
<td>0.680</td>
</tr>
<tr>
<td>Family medicine</td>
<td>2 (0.0)</td>
<td>1 (0.0)</td>
<td>1.000</td>
</tr>
</tbody>
</table>
**Supplementary Table 2.** Multivariable logistic regression analysis of mechanical ventilator use

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (95% confidence interval)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.01 (1.00–1.01)</td>
<td>0.039</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.99 (0.99–1.00)</td>
<td>0.002</td>
</tr>
<tr>
<td>White blood cells</td>
<td>1.05 (1.03–1.06)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>1.12 (1.07–1.18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Albumin</td>
<td>0.62 (0.51–0.75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.06 (1.01–1.11)</td>
<td>0.025</td>
</tr>
<tr>
<td>Lactate</td>
<td>1.16 (1.13–1.20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>After COVID-19</td>
<td>0.45 (0.36–0.56)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Multivariable adjustment for confounding variables that were significant in univariate analysis. Variables yielding P-values less than 0.1 in univariate analysis were entered into a backward multivariable logistic regression analysis.
**Supplementary Table 3.** Multivariable logistic regression analysis of vasopressor use

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (95% confidence interval)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.01 (1.01–1.02)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.32 (1.08–1.60)</td>
<td>0.005</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1.65 (1.05–2.60)</td>
<td>0.031</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>0.28 (0.13–0.64)</td>
<td>0.002</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.98 (0.98–0.99)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>White blood cells</td>
<td>1.05 (1.04–1.06)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>1.11 (1.07–1.15)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Albumin</td>
<td>0.38 (0.32–0.44)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.09 (1.05–1.13)</td>
<td>0.025</td>
</tr>
<tr>
<td>Lactate</td>
<td>1.21 (1.17–1.24)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>After COVID-19</td>
<td>0.77 (0.65–0.91)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Multivariable adjustment for confounding variables that were significant in univariate analysis. Variables yielding P-values less than 0.1 in univariate analysis were entered into a backward multivariable logistic regression analysis.
**Supplementary Table 4.** Multivariable logistic regression analysis of continuous renal replacement therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (95% confidence interval)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>1.37 (1.01–1.87)</td>
<td>0.044</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2.58 (1.39–4.79)</td>
<td>0.003</td>
</tr>
<tr>
<td>White blood cells</td>
<td>1.02 (1.00–1.04)</td>
<td>0.035</td>
</tr>
<tr>
<td>Platelets</td>
<td>0.99 (0.99–0.99)</td>
<td>0.002</td>
</tr>
<tr>
<td>Albumin</td>
<td>0.60 (0.47–0.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.34 (1.28–1.41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lactate</td>
<td>1.23 (1.18–1.28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>After COVID-19</td>
<td>0.71 (0.51–0.97)</td>
<td>0.031</td>
</tr>
</tbody>
</table>

Multivariable adjustment for confounding variables that were significant in univariate analysis. Variables yielding P-values less than 0.1 in univariate analysis were entered into backward multivariable logistic regression analysis.
Supplementary Table 5. Multivariable logistic regression analysis of intensive care unit admission

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (95% confidence interval)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td>0.99 (0.99–0.99)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Heart rate</td>
<td>1.00 (0.99–1.00)</td>
<td>0.021</td>
</tr>
<tr>
<td>White blood cells</td>
<td>1.06 (1.04–1.07)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>1.10 (1.07–1.14)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Albumin</td>
<td>0.69 (0.61–0.78)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.10 (1.07–1.14)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Lactate</td>
<td>1.27 (1.23–1.31)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>0.97 (0.94–0.99)</td>
<td>0.016</td>
</tr>
<tr>
<td>After COVID-19</td>
<td>0.86 (0.74–1.01)</td>
<td>0.060</td>
</tr>
</tbody>
</table>

Multivariable adjustment for confounding variables that were significant in univariate analysis. Variables yielding P-values less than 0.1 in univariate analysis were entered into backward multivariable logistic regression analysis.
Successful full-term delivery after out-of-hospital cardiac arrest during the second trimester of pregnancy: a case report

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Out-of-hospital cardiac arrest in pregnancy is extremely rare. In this case report, a 43-year-old female patient at 24.0 weeks of gestation collapsed outside her home after cardiac arrest. The paramedics performed cardiopulmonary resuscitation with defibrillation for ventricular fibrillation. Spontaneous circulation was achieved after 19 minutes. The fetus was stable during postarrest care. The patient exhibited high blood pressure with seizure-like symptoms for 2 days afterwards, which resolved with magnesium sulfate. She gradually recovered and returned to her daily activities while on treatment with beta blockers for cardiomyopathy and premature ventricular contractions until delivery. At 37.2 weeks of gestation, she underwent elective Cesarean section under spinal anesthesia. The baby weighed 2.55 kg and did not present with any complications. Here, we report a case of successful full-term delivery in a patient who underwent cardiopulmonary resuscitation for sudden cardiac arrest during the second trimester of pregnancy.

Keywords Heart arrest; Cardiopulmonary resuscitation; Pregnancy; Term birth; Case reports

Capsule Summary

What is already known
Cardiac arrest in pregnant women is extremely rare. There are some available treatments, such as a perimortem Cesarean delivery or hypothermia therapy. However, stability is not guaranteed. Hence, recommendations cannot be equally applied to all pregnant women.

What is new in the current study
After appropriate initial resuscitation, a pregnant woman who experienced out-of-hospital cardiac arrest during the second trimester achieved spontaneous circulation. The patient was able to maintain her pregnancy while receiving suitable treatment. To our knowledge, this is the first report of a case in Korea in which the patient successfully delivered her baby at full term after out-of-hospital cardiac arrest.
INTRODUCTION

Cardiopulmonary arrest in pregnancy is rare; it occurs in 1:12,000 admissions for delivery [1]. The incidence of out-of-hospital cardiac arrest (OHCA) in pregnant women is lower than that of in-hospital cardiac arrest [2]. Only a few OHCA cases have been reported worldwide. The maternal survival rate after OHCA is approximately 12% to 16% [2–10]. Despite its rarity, the low survival rates of this condition indicate that appropriate guidelines and training are required for such events. However, there is no scientific evidence for managing cardiac arrest during pregnancy. Because clinicians must simultaneously manage the patient and the fetus, cardiac arrest management in pregnancy is challenging. Here, we report the first case of successful full-term delivery in a Korean patient who received appropriate initial cardiopulmonary resuscitation for OHCA and who achieved spontaneous circulation at 24.0 weeks of gestation.

CASE REPORT

An unidentified pregnant woman was witnessed to collapse because of cardiac arrest. The paramedics arrived at the site 6 minutes after the event occurred. They activated the basic life support system and found that the initial heart rhythm was ventricular fibrillation. They shocked her heart five times with an automated external defibrillator. Another 6 minutes later, the specialist paramedics applied the adult-advanced life support system. They administered 1 mg of intravenous epinephrine and 500 mL of normal saline during the resuscitation. Following this, a supraglottic airway device (i-gel; Intersurgical Ltd., Wokingham, UK) was inserted. Eventually, return of spontaneous circulation (ROSC) was achieved 19 minutes after the start of active basic life support (Fig. 1).

The paramedics and the patient arrived at the hospital 34 minutes after the cardiac arrest. Based on the initial neurological examination, the patient was comatose (Glasgow Coma Scale score, 5). Her blood pressure was 176/100 mmHg, and her peripheral oxygen saturation was 100% on manual ventilation. The 12-lead electrocardiogram showed sinus tachycardia (131 beats per minute [bpm]). Because she was already unconscious, she was ventilated with an endotracheal tube and only 100 mg of suxamethonium and no additional sedatives. The patient’s cardiac ejection fraction (EF) was only 37%. After a few minutes, her heartbeat became irregular with premature ventricular complexes (PVCs) and tachycardia (150–160 bpm), for which 150 mg of amiodarone was administered. The patient also experienced short but repeated tonic seizure-like symptoms. To control the tonic seizure and rigidity, 2 to 5 mg of lorazepam and midazolam were alternately administered, to totals of 8 mg lorazepam and 10 mg midazolam. A computed tomography scan of the head, chest, and abdomen was performed in the emergency room, and the results were normal.

During the emergency rescue, no information was available regarding the patient’s duration of gestation. Her gravid uterus was at the level of the umbilicus. Hence, we assumed that she was approximately 20 weeks pregnant. The fetal cardiac activity was 160 to 170 bpm, and the fetal abdominal circumference on transabdominal ultrasonography was 194 mm, which is normal.

Fig. 1. Serial electrocardiogram monitoring. (A) Ventricular fibrillation was the initial heart rhythm. (B) The heart rhythm after the fifth defibrillation. (C) Return of spontaneous circulation 19 minutes after initiating active cardiopulmonary resuscitation. (D) A normal sinus rhythm in the patient upon hospital arrival.
for 24 weeks of gestation. The fetus had no abnormalities in the umbilical and middle cerebral arteries on Doppler ultrasonography. Moreover, there was no heartbeat deceleration during postarrest care in the emergency room. Therefore, we focused on the patient, and an emergency Cesarean section was not considered.

The patient was 43 years old and was at 24.0 weeks of gestation (gravida 5, para 1). After admission to the intensive care unit, she received sedative agents until absence of irritability. Furthermore, magnesium sulfate was administered for 6 days because eclampsia was suspected due to her symptoms, such as seizure-like motion, high blood pressure, and a urinary protein level of 3+. Her vital signs gradually stabilized, with the fetus remaining in a stable condition. All laboratory results were normal. Electroencephalography was performed to assess consciousness, and the findings revealed no abnormalities in background brain activity. The patient’s level of consciousness improved without any additional seizure-like symptoms. Therefore, she didn’t receive therapeutic hypothermia.

However, the echocardiographic evaluation showed an EF of 34.6% and dilated cardiomyopathy. Thus, the patient was treated daily with 100 mg metoprolol, a beta blocker for cardiomyopathy and PVCs until delivery. There were no other complications, and the patient and her baby were followed up at an outpatient clinic. At 37.2 weeks of gestation, she underwent elective Cesarean section under spinal anesthesia. The patient gave birth to a male infant weighing 2.55 kg (15th percentile) with an Apgar score of 7 after 1 minute and 8 after 5 minutes. After delivery, the baby underwent brain sonography and echocardiography, and the results showed no abnormalities. Subsequently, the patient and her son were discharged without any complications.

The Institutional Review Board at of Jeju National University Hospital approved this study (No. 2022-03-016). Informed consent for publication of the research details and clinical images was obtained from the patient.

**DISCUSSION**

In previous studies of pregnant women with OHCA, the maternal and neonatal survival rates were 28.6% (8 of 28) and 25.0% (7 of 28), respectively. Of these 28 total patients, four experienced sudden cardiac arrest during the second trimester of pregnancy. However, only one had a successful full-term delivery without maternal or neonatal complications after OHCA during the second trimester of pregnancy [6].

Although the incidence of OHCA in pregnancy is low, several methods can be used to increase patient survival rates during these emergencies. Early ROSC after cardiac arrest indicates a good prognosis for both the mother and the fetus. To decrease the time required to achieve ROSC in pregnant patients, high-quality resuscitation with aortocaval blood circulation against a gravid uterus and urgent transport are important [1,2,11]. The 2020 American Heart Association guidelines recommend that paramedics apply a new cardiac arrest algorithm and prioritize treating pregnant women [11]. In particular, a gravid uterus in a woman at more than 20 weeks of gestation compresses the aorta and vena cava and reduces cardiac output. Hence, manual left lateral uterine displacement (LUD) is required to facilitate aortocaval blood circulation [1]. If ROSC is not achieved, perimortem Cesarean delivery (PMCD) is required immediately after hospital arrival [1,11,12]. PMCD within 5 minutes is an effective method to improve blood flow [1,11].

There are no data supporting the usefulness of manual LUD after ROSC. However, a previous study showed that the full left lateral decubitus position can reduce aortocaval compression [13]. Thus, the patient was placed in the left lateral decubitus position without manual LUD. Moreover, there are no guidelines for whether PMCD should be implemented after ROSC. Five-minute PMCD is not satisfactory in 93% of cases, even for in-hospital cardiac arrest [12]. Nonetheless, this procedure was not performed in any maternal OHCA cases [9]. The average duration of transport from the scene to the hospital was 94 minutes based on French data [2], and it was more than 30 minutes according to Canada data [9]. In this case, although the patient reached the hospital 28 minutes after the paramedics arrived, she survived. Maurin et al. [2] reported that a pregnant woman at 31 weeks of gestation with prehospital ROSC did not survive despite PMCD. Therefore, obstetricians should consider PMCD depending on the pregnant woman’s gestational status and the circumstances to which she is exposed during the emergency.

A multidisciplinary team should perform postarrest care after resuscitation if the patient has achieved ROSC without PMCD. Although therapeutic hypothermia can be considered after cardiac arrest (even in pregnant women), its effects on the fetus are unknown [1,11,13]. Two studies have reported successful use of therapeutic hypothermia [4,6]. In one case, fetal demise occurred during hypothermia [5]. In the current case, the patient experienced seizure-like motions on the 1st day of hospitalization. Thus, the use of therapeutic hypothermia was considered. However, after administration of magnesium sulfate to control the symptoms of eclampsia, the patient did not present with any symptoms and had normal electroencephalography findings. The patient made a successful recovery without the need for therapeutic hypothermia.

It is also important to consider the cause of cardiac arrest dur-
Successful delivery after OHCA during pregnancy

An accurate diagnosis via proper examination can help facilitate lifesaving therapies [1]. In this case, further echocardiography and electrocardiogram showed that the patient’s EF was 30% to 35%, and her left ventricle was dilated. Moreover, her heartbeat was irregular with PVCs. A cardiologist made the diagnosis of peripartum cardiomyopathy with underlying dilated cardiomyopathy. Patients with this condition have the highest mortality rate (2%–24%) [14]. Patients with an EF < 40% must undergo appropriate counseling and receive joint multidisciplinary care and appropriate medications [14]. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are contraindicated during pregnancy. The use of beta blockers in pregnant patients with an EF < 40% have been shown to improve symptoms and survival [14,15]. Therefore, in this case, the patient was treated with metoprolol, a beta blocker used for cardiomyopathy and arrhythmia.

Early delivery can be considered if there are signs of nonreassuring fetal status [1]. Nevertheless, there are no guidelines regarding the preferred type of delivery in a full-term pregnant woman with stable status after cardiac arrest. The EF of our patient did not improve to 40%. Thus, we performed elective Cesarean section at 37.2 weeks gestation under spinal anesthesia according to the 2018 European Society of Cardiology guidelines [14].

In conclusion, if OHCA occurs in pregnant women, maternal and fetal outcomes show remarkable improvement with early recognition of arrest and rapid initiation of maternal resuscitation. A multidisciplinary team can facilitate a safe full-term delivery if appropriate treatment is provided with consideration of the conditions of the pregnant women and their fetuses.

CONFLICT OF INTEREST

The authors have no potential conflict of interest to disclose.

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REFERENCES

Nebulized nitroglycerin in the emergency department

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NEBULIZED NITROGLYCERIN

Inhaled pulmonary vasodilators have been a common management option for patients with pulmonary hypertension. Massive pulmonary embolisms (PE) have a similar pathophysiology in which the abrupt increase in pulmonary artery pressure results in right ventricular (RV) failure and hemodynamic collapse. Decreasing pulmonary artery pressure decreases RV afterload and improves RV function. Preventing RV failure is critical in the management of such patients as they can rapidly decompensate. Although the effects are typically short-lived, pulmonary vasodilators are a useful adjunct for the temporization of RV function and can be utilized as a bridge to definitive interventions. Depending on the resources of the emergency department (ED), it may be difficult to utilize typical pulmonary vasodilators such as nitric oxide (NO) and epoprostenol within a reasonable timeframe to benefit a crashing patient. Nitric oxide, although it is becoming more common, is simply not available in the average ED. Epoprostenol requires complicated assembly that is limited to respiratory therapists, which has significant logistical limitations when resuscitating a hyperacute critically ill patient. A reasonable and effective alternative is nebulized nitroglycerin.

MECHANISM OF ACTION

Nitroglycerin is metabolized into NO. NO leads to an increase in cyclic guanosine monophosphate (GMP) in vascular smooth muscles and ultimately results in vasodilation. Nebulized nitroglycerin largely remains in the pulmonary vasculature and has strong local pulmonary effects...
without systemic side effects such as hypotension. Therefore, nitroglycerin is essentially liquid NO and has the same effect when it is nebulized into an inhaled form.

INDICATIONS

Nebulized nitroglycerin can provide benefits for a variety of patient presentations, including crashing pulmonary embolism, acutely decompensating pulmonary hypertension and profound refractory hypoxemia (Table 1). These patients have similar pathophysiology, which can be simplified to RV failure secondary to increased afterload in the pulmonary vasculature. Pulmonary vasodilation reduces the RV afterload and improves RV function. In addition, inhaled pulmonary vasodilators tend to be distributed to the well-ventilated alveoli, thus directing blood preferentially toward better ventilated areas and improving ventilation-perfusion mismatch [1].

As mentioned above, other departments may not have access to NO, and it may be unrealistic to assemble an epoprostenol circuit in a timely manner. However, all emergency departments should have nitroglycerin and a nebulizer readily available.

Although there are no randomized controlled trials comparing patient outcomes with and without nebulized nitroglycerin, there are small studies and case reports suggesting that nebulized nitroglycerin is effective in decreasing pulmonary pressure without impacting systemic hemodynamics.

For example, Yurtseven et al. [2] studied 100 stable patients with history of chronic pulmonary hypertension who were intubated after mitral valve surgery and found that a dose of 20 μg/kg of nebulized nitroglycerin caused a 43% decrease in pulmonary vascular resistance with no change in systemic vascular resistance.

Another study conducted by Mandal et al. [3] studied 40 stable patients with chronic pulmonary hypertension following cardiac surgery who received 2.5 μg/kg/min of nebulized nitroglycerin for 10 minutes and found a 40% decrease in pulmonary vascular resistance without affecting the systemic vascular resistance.

Kline et al. [4] studied the effects of NO in the management of intermediate risk PE regarding improvement of echocardiographic abnormalities such as RV hypokinesis and dilation, which was accomplished 29% more often versus the control group who received oxygen as a placebo (in addition to standard anticoagulation therapy). Although this is a smaller study that does not directly investigate nebulized nitroglycerin, it suggests that NO (nitroglycerin’s metabolite) can aid in the recovery of RV function.

DOSING AND LIMITATIONS

For a critically ill or crashing patient, the dose of nitroglycerin is 5 mg nebulized over 20 to 30 minutes and repeated as necessary [1]. The main limitation is the volume of medication that will fit in the nebulizer, which is 3 to 5 mL. Some formulations of nitroglycerin have a 1 mg/mL concentration, which achieves the desired dosage of 5 mg. The studies mentioned above utilize lower doses such as 20 μg/kg or 2.5 μg/kg/min and demonstrate a statistically significant reduction in pulmonary vascular resistance [2,3]. Therefore, even if your department does not carry the 1 mg/mL concentration, it is reasonable to nebulize 3 to 5 mL of the dilute nitroglycerin (200 or 400 μg/mL) and repeat dosing as needed. The duration of action of nebulized nitroglycerin is approximately 20 to 30 minutes. Finally, inhaled nitroglycerin should be used with extreme caution in those with profound left ventricular failure, as the decrease in pulmonary vascular resistance results in an increase in left ventricular preload. This may worsen cardiogenic pulmonary edema.

CONCLUSION

Patients with massive PE, decompensated pulmonary hypertension, and refractory hypoxemia are at high risk for deterioration.
Nebulized nitroglycerin can be a valuable therapeutic adjunct and therapeutic bridge that aims to reduce RV afterload, improve RV function, and promote recovery. This management approach has a practical advantage versus other pulmonary vasodilators since it is readily available in most EDs and can be promptly administered, as opposed to NO and epoprostenol, respectively. Although most of the supporting literature is extrapolated from the pulmonary hypertension and/or the NO literature, there is enough research to suggest a benefit without significant harm. Large randomized controlled trials are still necessary to demonstrate whether there is a difference in clinical outcomes when comparing nebulized nitroglycerin versus standard therapy alone.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conceptualization: all authors; Investigation: all authors; Visualization: NAU; Writing–original draft: NAU; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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Simulation in emergency medicine graduate medical education: a call to lead

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INTRODUCTION

Simulation-based medical education made its first considerable appearance in graduate medical education (GME) in the late 1980s, as Gaba and DeAnda began to pioneer the use of immersive simulation for anesthesia residents in operating rooms at Stanford University in California, USA [1]. Since that time, the needs of learners have continued to evolve as the apprenticeship model for medical education has shifted in favor of clinical skills training [2]. Simultaneously, the expectations of our patients have also changed. Whether it was ever acceptable to “practice” a trainee's first critical procedure on a patient is its own topic of debate, but expectations have changed regarding patient safety and the basic procedural skill levels required prior to performing these procedures [3]. In many ways, the classic medical mantra “see one, do one, teach one” can no longer be standard of care.

EVIDENCE FOR SIMULATION

Simulation-based medical education has grown rapidly over recent decades, as has the body of evidence to support its use for a variety of skills and competencies. This trend has been especially evident in emergency medicine (EM) training. Once rarely utilized, many EM training programs now implement some form of simulation or manikin-based simulators and there is strong evidence to validate this practice [4]. Moreover, effective simulation builds a strong foundation of clinical skills, and has positive downstream effects on patient care and objective health outcomes [5].

Implementation of high-fidelity systems and technology in simulation have shown favorable outcomes in EM resident learning, but simulation-based resident training is not limited to high-fidelity manikins or models [6]. Additional strategies, including table-top scenarios and in situ simulation, have been used to prepare for a variety of emergent scenarios including mass casualty training, hospital codes, and disaster drills. The in situ strategy has proven effectiveness in emergency departments for the development of protocols, improvement of teamwork, and provision of timely care [7].

The evidence for simulation in GME also extends to procedural skills training. There are a multitude of high acuity procedures that EM physicians must master in training, and this need only furthers the demand for procedural simulation as a key strategy in skill development. For example, relatively common procedures such as cardiopulmonary resuscitation, defibrillation, and cardiac arrest management have shown significant improvement after simulated training [8].
Reinforcing the trainee’s clinical procedure experience with simulation augments their exposure to lower frequency procedures, increases trainee success rates, and improves retention of skills [9]. Often referred to as “high frequency low acuity” procedures including pediatric intubation and transvenous pacing have also shown improved performance and mastery after a simulated curriculum [10,11]. The development of procedural skills and proficiencies via simulation has been shown to translate into improved trainee confidence and objective outcome measures [5,12].

Beyond technical skills and manikin-based teaching, simulation in EM has been successfully implemented in a variety of ways. It has proven effective in communication and health systems science [13]. It can activate learners’ emotional states, allowing them to develop cognitive and communication skills to improve their clinical practice. It can be effectively used in a virtual space to provide for remote learning opportunities, as exemplified during the COVID-19 pandemic [14]. We have also seen its use in resident remediation, allowing for performance improvement in a safe environment for both our trainees and patients [15].

At its very core, simulation allows emergency training programs the ability to address the needs of their learners. There is now a large body of evidence to demonstrate the utility of simulation in performing high-stakes procedures, caring for a variety of disease presentations, and developing team-based skills. Simulation allows mastery of these elements to be achieved under controlled conditions and in a safe environment, ultimately improving trainee performance and skill acquisition.

**SIMULATION AS A CORE REQUIREMENT**

Despite the growing body of evidence and our specialty’s reputation for pushing the envelope, EM is not the first or even the second medical specialty to consider the codification of simulation as a required component in residency training. For example, in the United States and as outlined by the Accreditation Council for Graduate Medical Education (ACGME), both the general surgery and internal medicine specialties implemented simulation as a core program requirement as early as 2006 [16,17]. In the interval, the general surgery ACGME has expanded these requirements to include a “simulation-based curriculum,” and general surgery programs are now mandated to designate an individual who is responsible for managing these activities [18]. Although simulation within EM residencies has seen tremendous growth and substantiation in the last few decades, the ACGME does not yet include simulation as a formally required component of resident education in EM [16]. The result is considerable variety in simulation education and delivery both in the United States and internationally where simulation requirements are not formalized or clear.

**CURRENT FIELD IN EMERGENCY MEDICINE**

With a growing abundance of high-quality evidence to support the need for simulation in GME, the time has come for medical simulation to become a standard, codified requirement in residency training. While the evidence suggests that all medical specialties would gain from inclusion of this educational format, EM residents and their patients are uniquely positioned to benefit from the adoption of this no longer novel educational strategy.

Emergency physicians are required to master a plethora of unplanned, high-stakes encounters and high acuity procedures. On any given shift, EM residents may be required to interview and examine a victim of a sexual assault or provide notification to a family member of an unanticipated death. On that same shift, time-sensitive and high-stakes procedures such as cardiopulmonary resuscitation, central line placement, and intubation may also be necessary. These encounters and procedures require a high level of competence and skill with no margin for error, and there is clear evidence that physician performance in these areas improves following simulated experiences [19,20].

Our patients deserve our best, and it is our moral imperative to deliver them the highest-quality care possible. Formalizing simulation as a core requirement in EM GME is the necessary next step.

**CONFLICT OF INTEREST**

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Euglycemic diabetic ketoacidosis: a potential pitfall for the emergency physician

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INTRODUCTION

Diabetic ketoacidosis (DKA) is a potentially life-threatening complication of diabetes mellitus that can occur in patients with type 1 or type 2 diabetes. The triad of hyperglycemia, metabolic acidosis with an increased anion gap, and ketosis heralds the familiar clinical presentation of DKA. The mechanisms involved in this metabolic disturbance are due to absolute or relative insulin deficiency. Euglycemic DKA (eu-DKA) was first described in 1973 and is characterized by ketoacidosis and electrolyte derangement with only marginal or absent elevation of serum glucose, often < 11.0 mmol/L (200 mg/dL) [1].

Although an uncommon diagnosis, the absence of hyperglycemia in eu-DKA poses a potential pitfall for the unsuspecting emergency physician, often leading to delays in diagnosis and commencement of treatment, carrying with it the potential for adverse metabolic consequences and increased mortality.

The aim of this article is to review the clinical presentation of eu-DKA and its pathophysiology and treatment.

CLINICAL PRESENTATION OF EUGLYCEMIC DIABETIC KETOACIDOSIS

Patients with eu-DKA typically present with symptoms such as malaise, dyspnea, nausea, vomiting, and abdominal pain, similar to patients with conventional DKA [2]. The most important step in diagnosis of eu-DKA is considering it as an option and not being falsely reassured by the presence of normoglycemia. Any patient with diabetes demonstrating these symptoms should be screened for eu-DKA with blood pH and blood or urine ketone testing, although eu-DKA may be the first presentation of diabetes.

A patient with eu-DKA will typically have normoglycemia in the presence of metabolic acidosis (pH less than 7.3) and decreased blood bicarbonate (less than 18 mmol/L) [2]. Serum and urine ketones must be elevated to qualify as eu-DKA [2].

Lactic acid may be elevated but should not be the sole reason for the increased anion gap. High lactate level in the absence of ketosis suggests that an alternative diagnosis should be sought.

Leukocytosis may be present with concurrent infection; however, it may result from hemoconcentration due to dehydration or a stress response associated with acute illness [2]. Other markers of infection should be sought before attributing it as the precipitating factor.
Total potassium level is often depleted in eu-DKA, but blood potassium may be normal. Mild hyponatremia may also be seen but is typically less marked than the “pseudohyponatremia” seen in profound hyperglycemic states [2].

**Epidemiology**

With reported incidences ranging from 2.6% to 3.2% of patients admitted with DKA [3], eu-DKA is a relatively uncommon diagnosis, with no demonstrable difference between sexes.

**Mechanisms of Euglycemic Diabetic Ketoacidosis**

It is believed that eu-DKA primarily occurs due to a carbohydrate deficit, which leads to increased lipolytic activity and subsequent ketoacidosis [2]. The causes of eu-DKA can be divided into two main groups: glucose wasting (due to such events as glucosuria or persistent vomiting) and low level of hepatic glycogen (due to such events as starvation and chronic alcoholism).

Typically, serum insulin level is low in eu-DKA patients, with an associated excess of counterregulatory hormones such as glucagon, cortisol, and adrenaline [2]. Significant volume depletion occurs due to osmotic diuresis from glucosuria, often further exacerbated by reduced oral intake and vomiting.

**Alcoholic ketoacidosis**

Alcoholic ketoacidosis should be considered a subclass of eu-DKA and carries a significant risk of mortality in patients with alcohol dependence [2]. Chronic alcohol consumption causes insulin resistance and destroys pancreatic beta cells [4]. These factors, combined with the effects of poor dietary intake, reduce the body’s storage of glycogen in the liver and the glucose reserve. Consequently, even short periods of fasting in individuals with chronic alcoholism can result in life-threatening ketoacidosis.

**Euglycemic diabetic ketoacidosis in pregnancy**

Maternal hormones, such as human placental lactogen and increased level of cortisol, contribute to increased insulin resistance in the pregnant patient [5]. Even overnight fasting can lead to increased fat breakdown and ketogenesis and is further compounded by the respiratory alkalosis that occurs during pregnancy. This decreases blood bicarbonate, reducing the body’s ability to buffer organic acids. These factors combine to increase the likelihood of ketoacidosis during pregnancy.

Consequently, short periods of starvation during pregnancy, such as those experienced during episodes of vomiting, decreased appetite, or intercurrent illness, lead to glucose depletion and ketogenesis, which may proceed to eu-DKA. Most documented cases of eu-DKA during pregnancy occurred in patients with type 1 diabetes [6]. However, there is a growing body of evidence reporting eu-DKA in patients with type 2 diabetes [7] and in nondiabetic pregnant women with intercurrent illnesses [8,9].

**SGLT2 inhibitors**

The year 2011 saw the introduction of sodium glucose transporter 2 (SGLT2) inhibitors, a class of drugs that includes dapagliflozin and canagliflozin, used in the management of patients with type 2 diabetes. Transport proteins in the proximal tubule of the kidney reabsorb glucose and sodium from urine independent of insulin. SGLT2 inhibitors block this mechanism, leading to glucosuria and natriuresis. Several benefits of SGLT2 inhibitors have been identified in therapeutic treatment of patients with diabetes, including better blood pressure management and improved glucose control. These drugs may also provide a cardiorenal protective role. However, since their launch, there have been several published case reports describing eu-DKA in patients treated with this class of drugs [10–12]. Initially used exclusively in the management of type 2 diabetes mellitus, the intended population for this group of drugs was expanded to include select patients with type 1 diabetes. However, due to the high incidence of DKA in this group [13], authorization for use in type 1 patients was withdrawn in the United Kingdom in December 2021 [14]. The US Food and Drug Administration (FDA) and the European Medicines Agency also issued warnings in 2015 and 2016, respectively, on predisposing factors to development of eu-DKA in patients with type 2 diabetes mellitus taking SGLT2 inhibitors [15].

The incidence of eu-DKA in patients with type 2 diabetes taking SGLT2 inhibitors is reported to be approximately 0.1% [16]. Data published by the FDA in 2021 reported the median time to ketoacidosis after initiation of SGLT2 inhibitor therapy was 43 days [15]. In a different case study, 50% of patients who developed eu-DKA while taking SGLT2 inhibitors had clear precipitating events, such as acute illness (e.g., infection and surgery), reduced oral intake, and reduced insulin dose [17]. Fralick et al. [18] reported that type 2 diabetes patients taking SGLT2 inhibitors are more than twice as likely to develop diabetic ketoacidosis within 180 days of follow-up compared with patients receiving other oral hypoglycemic agents.

**Treatment**

Early involvement of a multidisciplinary team including an experienced endocrinologist in the management of this patient group...
is paramount. The initial patient management is directed toward fluid resuscitation, as patients usually present with profound dehydration. Fluid resuscitation using intravenous crystalloid should continue until the anion gap and the acidosis have resolved [2].

In contrast to conventional DKA management, 5% dextrose should be added to the fluid resuscitation regime to avoid hypoglycemia and hasten the clearance of ketosis. An increase to 10% dextrose should be considered if ketoacidosis persists on 5% dextrose [3].

Given that patients in eu-DKA have blood glucose level less than 11.0 mmol/L (200 mg/dL), Modi et al. [19] suggest commencing insulin infusion at a rate of at least 0.02 to 0.05 units/kg/hr. Decreasing the rate further may result in insufficient insulin in patients with type 1 diabetes and may not aid in resolution of ketoacidosis. Other authors suggest starting the insulin infusion at a slightly higher rate [2]. Blood glucose level should be assessed hourly at first and electrolytes monitored every 4 hours as intravenous supplementation of potassium and other electrolytes may be required [2].

Patients taking SGLT2 inhibitors should discontinue these medications as soon as the diagnosis is recognized and should not be restarted until the patient has fully recovered from the acute illness [12]. Sodium bicarbonate infusions are not indicated, and their use in the setting of severe acidemia (pH less than 6.9) is controversial [2].

CONCLUSION

For an unsuspecting emergency physician, eu-DKA is a diagnostic challenge, primarily due to the absence of hyperglycemia. Understanding the various mechanisms that lead to eu-DKA and the various contexts in which it can occur, particularly the at-risk groups, will increase consideration of eu-DKA as a potential diagnosis. Treatment focuses on aggressive hydration, glucose replacement, insulin administration, and correction of any electrolyte imbalance, as well as treating the precipitating cause.

Morbidity and mortality can be significantly improved by early diagnosis and initiation of treatment [2]. Intercurrent illness, prolonged vomiting, chronic alcoholism, and SGLT2 inhibitors must be considered as potential triggers for eu-DKA in patients presenting with acidosis and an increased euglycemic anion gap, remembering that pregnant women and the malnourished are especially at risk.

Introduction of SGLT2 inhibitors has highlighted the diagnosis of eu-DKA. Due to the favorable cardiorenal protective effects of these drugs, their use is expected to increase significantly among patients with type 2 diabetes. To support this, appropriate education of both the patients and physicians, including those in the emergency department, should take place to ensure eu-DKA is considered as a diagnosis and timely treatment is commenced in patients taking this class of drugs.

CONFLICT OF INTEREST

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Acute subclavian artery occlusion mimicking cerebral infarction

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A 92-year-old female patient presented to the emergency department with sudden onset of left-arm weakness. Initial neurological examination revealed grade II motor weakness in the left upper extremity. Brain computed tomography showed no hemorrhage, and diffusion-weighted image showed no definite acute infarction (Fig. 1A). However, magnetic resonance angiography revealed a left subclavian artery occlusion (Fig. 1B). On physical reexamination, we found that her left arm was pale and cold, the brachial pulse was very weak, and the radial pulse was not palpable. Additional upper extremity computed tomography angiography was performed. Computed tomography angiography showed an abrupt contrast filling defect of the left subclavian, axillary, and forearm arteries, and we could partially visualize the axillary artery from the middle of the humerus to the elbow level (Fig. 1C, D). The patient’s symptom of left arm weakness was suspected to be due to subclavian artery occlusion. The patient was transferred to a vascular surgeon and underwent an emergency arterial thrombectomy (Fig. 2). After the surgery, the patient’s arm weakness and sensation improved, and she was discharged without complications.

Common conditions that mimic stroke include seizures, toxins, hypoglycemia, syncope, psychiatric disorders, brain tumors, and spinal cord lesions [1,2]. This report presents an unusual case of a patient with acute subclavian arterial occlusion that presented as a stroke mimic. We recommend that patients suspected of having a stroke with acute hemiparesis be examined thoroughly for cold skin, pulselessness, weak pulse, pale skin color, and paresthesia to evaluate arterial occlusive disease. Informed consent for publication of the research details and clinical images was obtained from the patient.

CONFLICT OF INTEREST

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Capsule Summary

What is already known
Several clinical conditions can mimic ischemic stroke.

What is new in the current study
Upper limb weakness can be caused by subclavian artery occlusion. Patients with acute hemiparesis have to be evaluated for arterial occlusive disease.
Fig. 1. Magnetic resonance imaging and computed tomography angiography of the patient. (A) Diffusion-weighted image shows no definite cerebral infarction. (B) Magnetic resonance angiography shows left subclavian arterial occlusion (arrow). (C, D) Computed tomography angiography shows an abrupt contrast filling defect of left subclavian, axillary, and forearm arteries. Partially visualized axillary artery from the middle of the humerus to elbow level (arrow).

Fig. 2. Thrombus material obtained during surgical thrombectomy.

AUTHOR CONTRIBUTIONS

Conceptualization: SKO; Data curation: SKO; Formal analysis: SUC; Investigation: SUC; Methodology: SKO; Project administration: SKO; Resources: SUC; Software: SUC; Supervision: SKO; Validation: SUC; Visualization: all authors; Writing–original draft: all authors; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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Underlying mucus plugging during central line placement: a time-sensitive diagnostic dilemma

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Dear Editor,

Superimposed clinical scenarios present diagnostic dilemmas that may delay care and ultimately increase morbidity and mortality. We report a case illustrating therapeutic ambiguity in the setting of central line placement with underlying mucus plugging of the right mainstem bronchus in a critically ill patient. The requirement for informed consent was waived due to the retrospective nature of the study.

In critically ill patients and postoperative patients with impaired cough reflex, an imbalance between mucus production and clearance occurs [1]. Despite diligent respiratory care, this imbalance may eventually lead to clinically significant mucus plugging, increasing morbidity and mortality [2]. When combined with invasive procedures such as central line placement, clinical management can become challenging, leading to diagnostic and therapeutic uncertainty.

A 62-year-old female patient with a history of combined liver-kidney transplant 19 years prior to admission presented with small bowel perforation. She underwent staged bowel resection and abdominal closure on day 1 and day 3, respectively, and was subsequently extubated. Postextubation, the patient had a normal chest X-ray. On hospital day 5, due to a lack of peripheral access and ongoing need for intravenous resuscitation, a central venous catheter was placed into the right internal jugular vein under ultrasound guidance without issue using the standard Seldinger technique. The patient was stable both hemodynamically and from a respiratory standpoint before, during, and after the procedure. However, on the postprocedure chest film, the right hemithorax was found to be opacified. This led to an unexpected clinical conundrum.

Physical examination of the chest demonstrated asymmetric thoracic movement and absent breath sounds on the right hemithorax. Hemothorax as a line-related complication was initially considered given the patient’s clinical course. We decided to proceed with bedside ultrasound of the thorax in anticipation of aspiration with possible tube thoracostomy. However, ultrasound failed to identify any fluid in the right hemithorax. Because of the patient’s hemodynamic stability chest computed tomography (CT) was performed, and showed appropriate central line placement and a large mucus plug in the right mainstem bronchus, causing collapse of the right lung with rightward tracheal deviation. Pulmonology performed a bedside bronchoscopy with evacuation of the mucus plug from the right mainstem. The remainder of the patient’s hospital course was uneventful, barring postoperative ileus, and she was discharged on hospital day 13. Figs. 1–4 show the preprocedure X-ray, postprocedure X-ray, chest CT, and post-bronchoscopy chest X-ray.
Before the widespread use of ultrasound guidance, immediate complication rates post-central line insertion are between 6.3% and 11.8%, with these rates decreasing to 4.0% to 7.0% with ultrasound use [3,4]. Hemothorax following central line placement is a known complication. Central line placements in a surgical unit are mostly placed by surgical trainees who are also first responders to correlating a radiological finding on their patients.

New imaging findings post-central line insertion similar to our patient can often pose a diagnostic dilemma and a decision-making challenge for young surgical trainees on call. A mistaken working diagnosis of hemothorax following central line insertion with opacification of the right hemithorax on chest X-ray can lead to an unnecessary tube thoracostomy in an unstable patient [4].
Mucus plugs can accumulate from desquamating mucus cells of the bronchus and lead to mechanical airway obstruction in postoperative patients, especially those with reduced cough capacity [1]. Occlusion by a mucus plug in the larger upper airway can lead to complete lung collapse, as seen in our case. Thoracic X-ray can be diagnostic when not confounded by any other thoracic intervention. Thoracic CT can be useful when the diagnosis is unclear. Bronchoscopy is usually both diagnostic and therapeutic [5].

While the dilemma in our example was ultimately innocuous and the patient improved, suspicion should remain high for such indolent processes in critically ill patients due to limited reserve and potential morbidity and mortality.

CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

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A case of malignant atrophic papulosis with septic complications

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Dear Editor,

We would like to share the interesting case of a 38-year-old woman who presented to the emergency department of an outside hospital with a rash accompanied by severe abdominal pain, diarrhea, and fever. The rash had been intermittent for 2 years, was located over the neck, trunk, arms, and legs, and was not accompanied by tenderness or itching. Skin biopsy and pathological examination performed 1 year prior showed partial epidermal atrophy, local fibrous hyperplasia and hyaline degeneration of the dermis, and multiple mucus deposits between surrounding collagen, at which point a diagnosis of Degos disease was made. The patient experienced prominent recurrence of the rash in the preceding 20 days. The patient denied cough, sputum, headache, paralysis, or paresthesia. Based on her history and test results, a diagnosis of malignant atrophic papulosis (MAP) and acute peritonitis with ascites was made at the local hospital. After receiving ceftriaxone and glucocorticoids, her condition did not improve significantly. She was transferred to our emergency department. The patient was conscious with a Glasgow Coma Scale of 15 and her vital signs were temperature 38.9 °C, heart rate 137 beats/min, respiratory rate 33 breaths/min, blood pressure 107/73 mmHg, and pulse oximetry 99% on room air. Physical examination showed generalized, painless, nonpruritic, ring-shaped pigmented plaques, the majority of which were crusted over, particularly the scattered abdominal lesions (Fig. 1).

The patient’s white blood cell count was elevated (11.35 × 10⁹/L), as was procalcitonin (0.51 ng/mL). Chest and abdominal computed tomography revealed a thickened intestinal wall, swollen mesentery, ascites, bilateral pleural effusion, and diffuse bilateral pulmonary consolidation (Fig. 2). The patient was COVID-19 negative. A peripheral smear and culture of the patient’s abdominal fluid revealed increased mesothelial cells, eosinophils, neutrophils, and lymphocytes, without tumor cells. Blood culture results from the outside hospital were positive for Enterococcus faecium and Enterococcus avium (received on the 1st day after admission).

The patient’s history, physical examination, and blood and culture results suggested a diagnosis of MAP and sepsis from intestinal inflammation with ascites and pneumonia. Methylprednisolone (40 mg/day), heparin (5,000 U/day), and imipenem were immediately initiated. The gastrointestinal (GI) team found no signs of intestinal perforation or necrosis and thus surgery was not recommended. Immunotherapy against C5 (e.g., eculizumab) was refused by the patient and her family. She clinically deteriorated, developing respiratory failure and shock on treatment day 2.
In compliance with her family’s wishes, the patient was discharged home without exploratory laparotomy. She expired 2 days later.

This study is in compliance with the Declaration of Helsinki. It was approved by the Human Ethical Committee of West China Hospital of Sichuan University (No. 2,019,201). Written informed consent for publication of the research details and clinical images was obtained from the patient’s parents.

Degos disease is a rare, multisystem, immune-related vasculopathy with a cutaneous form (benign atrophic papulosis) and a systemic variant, MAP [1]. Approximately 200 cases have been reported in the literature [2]. Lesions may appear at different stages in various locations, with the trunk being the most common. The GI tract and the central nervous system are most often affected in MAP, though there are reports of possible involvement of other organs, such as the respiratory system and the eyes [3]. Common causes of death include GI perforation leading to hemorrhage and cerebrovascular accidents [3,4]. The underlying mechanisms of the systemic manifestations of Degos disease are not well understood [5]. One hypothesis is that ischemia-induced proliferation and swelling of endothelial cells with dysregulated C5–9 membrane attack complexes may be responsible [6]. The diagnosis of atrophic papulosis is made clinically and supported by histologic findings [3]. The median survival time of MAP is 2 to 3 years; the 5-year survival rate is < 50% [7]. Intestinal perforations are uncommon in MAP (up to 2.1%) [8]. Almost 60% of cases of death are due to the most common complications, which are peritonitis caused by intestinal perforation and cerebral infarction [9].

In this patient, the diagnosis and treatment of sepsis were delayed given her initial presentation at an outside hospital. We lost the opportunity to administer antibiotics in a timely manner in line with the surviving sepsis campaign [10]. Notably, there is no proven therapy against MAP. Immunosuppressants, anticoagulants, and antiplatelet medications are the first-line therapeutic approach in newly diagnosed patients. Eculizumab is a salvage therapy in critically ill MAP patients [6], but there is questionable mortality benefit in patients with perforation [9]. Our patient’s sporadic use of prednisone limited steroidal efficacy against vascular inflammation. It is likely that our patient developed systemic symptoms from destabilized gastrointestinal lesions, leading to peritonitis and sepsis, i.e., life-threatening organ dysfunction caused by a dysregulated host response to infection [10]. Our patient did not undergo laparotomy. Numerous reports have documented patient death from MAP despite surgical interventions [9,11,12]. Therefore, whether surgery is a definitive, efficacious treatment for MAP warrants further exploration.

In conclusion, the prognosis for systemic MAP is poor, especially when the gastrointestinal system is involved. No therapy...
with substantial mortality benefit has been established. Early identification and appropriate sepsis management remain the best practice. Timely medical treatment of MAP and its complications is a significant challenge. Emergency physicians and dermatologists must remain vigilant for serious complications when treating Degos disease, particularly sepsis.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conceptualization: MT, YH; Data curation: YH, KZ; Funding acquisition: YH; Investigation: MT, KZ, YH; Resources: MT, KZ, YJ; Supervision: YH, KZ, YJ, BLW; Writing–original draft: MT, KZ, YH; Writing–review & editing: YH, YJ, BLW. All authors read and approved the final manuscript.

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Star in the storm: percutaneous stellate ganglion blockade for drug-refractory electrical storm in the emergency department

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Dear Editor,

Electrical storms are an increasingly common presentation, especially in the developing world, where the incidence of coronary artery disease continues to increase. Prompt resuscitation and emergency care for these patients are critical and can determine whether they survive or not.

We would like to highlight two scenarios where refractory ventricular arrhythmias were successfully treated with ultrasound-guided (USG) stellate ganglion block (SGB). Informed consents for publication of the research details and clinical images were obtained from the patients.

The first was a 68-year-old female patient who presented to the emergency department (ED) with acute-onset palpitations and unresponsiveness for the last 1 hour. She had a history of extensive anterior wall myocardial infarction and had undergone percutaneous coronary intervention 2 years prior. She had a history of similar palpitations in the previous 1 year, for which she received electrical cardioversion. She also had a history of high-grade fever with a cough over the 2 days prior to presentation. Her other comorbidities included hypothyroidism, diabetes mellitus, and hypertension.

On arrival, she was tachycardic with a heart rate of 220 beats/min and without recordable blood pressure. Her electrocardiogram revealed a monomorphic ventricular tachycardia (VT) that was promptly cardioverted at 100 J and returned to a normal sinus rhythm. Hypokalemia and hypomagnesemia were excluded as the triggering etiology on laboratory investigations. She experienced another episode of unstable VT, for which multiple episodes of cardioversion at 200 J failed. She was subsequently treated with amiodarone (bolus and infusion) and propranolol. After no response, the patient was administered intravenous lidocaine 1.5 mg/kg. Over the next 10 minutes, the patient’s dyspnea increased, and she was treated with ventilatory and vasopressor support. She was sedated and paralyzed to decrease sympathetic stimulation. In view of sustained VT that was not electrical or chemical cardioversion, the decision was made to proceed with a bilateral SGB. With ultrasound guidance, approximately 8 mL of 0.2% ropivacaine was placed into the anterior surface of the longus coli muscle at the level of the C6 vertebra by a trained emergency medicine physician (EP) (Fig. 1). Eight minutes after this procedure, the VT subsided and reverted to a regular sinus rhythm.

The patient later tested positive for COVID-19 and was shifted to the isolation intensive care unit (ICU) for further care. She experienced no further episodes of VT. However, she progressed to septic shock secondary to pneumonia and passed away.

The second case was that of a 42-year-old diabetic male patient with ischemic cardiomyopa-
The man presented to the ED with chief complaints of chest pain and profuse sweating for the past day. He had a history of coronary artery bypass graft to the left anterior descending and left circumflex arteries 2 years prior. His heart rate was 198 beats/min, and his blood pressure was 90/60 mmHg. His respiration rate was 32 breaths/min, and he had a peripheral oxygen saturation of 88% on room air. Further examination revealed an elevated jugular venous pressure and bilateral crepitations. Cardiac monitoring showed a monomorphic VT, for which he received multiple attempts at synchronized cardioversion, which failed to convert the rhythm. After the second cardioversion, the patient experienced a brief episode of ventricular fibrillation, and defibrillation was carried out at 200 J followed by return of a pulse.

Antiarrhythmics of intravenous lidocaine, amiodarone, and metoprolol therapy were also ineffective. The patient was placed in the supine position with the neck extended and the head turned to the right side. Under portable USG, 6 mL of 1% lignocaine was placed anterolaterally into the longus coli muscle by the EP. Gentle pressure was applied to facilitate caudal spread of the anesthetic to reach the C7 to T1 level. Horner syndrome confirmed success of the block. Resolution of VT on the cardiac monitor started at 6 minutes and lasted 8 hours. A repeat episode at that point was successfully converted by electrical cardioversion. The patient was eventually transferred to the ICU for further management, and he remained free of arrhythmia for the remainder of his ICU stay.

Electrical storms (ESs), one of the most lethal of all cardiac arrhythmias, are defined by ≥ 3 episodes of sustained VT, ventricular fibrillation, or appropriate shocks from an implantable cardioverter defibrillator within 24 hours [1].

ESs are usually associated with undesirably high levels of sympathetic stimulation, which is only worsened by repeated attempts at electrical cardiac resynchronization therapy. The presence of an old infarct and scar tissue leads to increased propensity for electrical instability [2]. ESs are associated with significant morbidity and mortality and often require aggressive treatment to increase chances of survival and recovery [3].

In treatment of ES, simultaneously stabilizing the hemodynamic status and correcting the underlying cause should be prioritized. It is often difficult to identify a specific trigger of ES. It may be precipitated by acute myocardial ischemia, electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hyperkalemia), worsening heart failure, sepsis, and poor compliance with antiarrhythmic medications [4,5]. Antiarrhythmic medication along with β-blockers (intravenous propranolol) remain the standard treatment for ES, although evidence has shown esmolol also to be effective [6,7].

An SGB was initially considered to address ventricular arrhythmias because most sympathetic innervation to the heart occurs through the postganglionic fibers of the right and left stellate ganglia. Myocardial infarctions may lead to partial denervation of these fibers and paradoxically induce a supersensitivity to catecholamines, increasing heart vulnerability to the electrical induc-
Stellate ganglion block for electrical storms

Sympathetic denervation counteracts this pathological process by reducing the amount of norepinephrine released at the ventricular level and increasing the ventricular fibrillatory threshold [9].

A retrospective study of 30 patients with drug-refractory ES concluded that percutaneous bedside USG SGB is a safe procedure and must be considered to stabilize ventricular arrhythmia [10]. This position was further strengthened by a 2017 systematic review by Meng et al. [11], which concluded that SGB is very effective for acute treatment of ES. Nademanee et al. [2] compared traditional antiarrhythmic therapy to cardiac sympathetic blockade (via SGB) and showed that the latter is far superior in treating ES. This finding has led to the recommendation that SGB always be considered in cases of drug-resistant electrical storm.

A variety of other therapies (including neuromodulation with thoracic epidural anesthesia, spinal cord stimulation, or cardiac sympathetic denervation) can also yield a curative effect in certain situations when standard treatments are inefficacious [5]. However, these procedures are often beyond the scope of services available in an ED. SGBs were traditionally performed by anesthesiologists and pain management specialists across the country. With the advent of EPs trained in USG blocks, the role of peripheral nerve blocks in the ED is increasing beyond the typical use in pain management. Thorough knowledge of neck anatomy, appropriate needle tracking, and steady hand-eye coordination coupled with regular practice provide a short learning curve for these relatively safe and life-saving procedures [12].

The authors would like to highlight the need for recognition of alternative treatment modalities such as SGB, which may be potent additions to the EP toolbox in management of drug-refractory ventricular arrhythmias. USG SGB is a step toward minimally invasive resuscitation that can be performed at the bedside by trained EPs to reduce the ventricular arrhythmia burden in an acute stage.

CONFLICT OF INTEREST

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