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The prehospital emergency medical service system in Korea: its current status and future direction

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INTRODUCTION

In 2022, the number of prehospital emergency medical service (EMS) calls in Korea reached 3.61 million, resulting in two million transports, which was twice the number recorded in 2002. The increasing demand for EMS transport is accompanied by public demand for safe and effective EMS care. Quality measurement is fundamental for improving EMS systems. This commentary introduces the current status of the Korean EMS system and its quality measurement and discusses the future direction of the EMS system with a focus on quality measurement.

THE KOREAN EMS SYSTEM

Korea’s fire-based public EMS system is exclusively operated by the National Fire Agency of Korea (NFA) and has 18 provincial fire departments and dispatch centers. A designated call number of 119 is used for EMS, fire, and rescue calls. Medical directors at dispatch centers provide online medical directions 24/7/365 for EMS providers’ requests for services, such as advanced airway management, fluid administration, cardiopulmonary resuscitation (CPR) withdrawal, drug administration, and complex problems at the scene. Dispatcher-assisted bystander CPR began in 2011 [1], and video instruction became available in 2017 [2]. In 2022, 13,896 EMS providers and 1,625 ambulances were operating nationwide. Each ambulance run is attended by two or three EMS providers, with 63% of all runs being attended by three EMS providers in 2022. Multiple dispatches for cardiac arrest and severe trauma were introduced in 2015 [3], and 79% of cardiac arrest patients and 38% of severe trauma patients received multiple dispatches in 2022. Most multiple dispatches consist of multiple ambulances of the same service level, but 5% of multiple dispatches for cardiac arrest and 20% for severe trauma were by a fire engine (pumbulance) in 2022. EMS providers in Korea include emergency medical technicians (EMTs), who are classified as advanced or basic, and nurses. Most advanced EMTs (AEMTs) graduate from EMT schools (3–4-year courses) and must also pass the national certification examination. Nurses and AEMTs provide prehospital advanced cardiac life support, including advanced airway management and fluid administration under online medical direction. In 2022, 66% of EMS providers were AEMTs.
or nurses, and ambulance teams with AEMTs or nurses responded to 97% of calls. Because of the limited scope of practice for EMTs, the use of prehospital epinephrine in cardiac arrest has not been systemically implemented, but pilot projects, including the Smart Advanced Life Support program (which began in 2016 and has been supported by the Ministry of Health and Welfare of Korea) [4] and the nationwide designated response for severe disease program of the NFA (started in July 2019), have made significant progress [3]. In 2023, the Central EMS Committee expanded the scope of practice for EMTs to include prehospital epinephrine administration.

EMS QUALITY MEASUREMENT

The main data sources for EMS quality measurements are the EMS run sheet and the in-depth EMS registry for severe diseases. Under the Act on 119 Rescue and EMS, all EMS providers should record ambulance run sheets for all dispatches. The ambulance run sheet collects basic ambulance operational information, chief complaints, patient’s clinical status, field management, transported hospitals, and medical direction. There are three in-depth EMS registries for severe diseases: the EMS out-of-hospital cardiac arrest registry (started in 2011), the EMS Severe Trauma Registry (started in 2012), and the EMS Cardiovascular Registry (started in 2013). The collected information includes Utstein variables in the EMS Out-of-Hospital Cardiac Arrest Registry [5]; field triage decisions [6], field trauma care, and heli-EMS in the EMS Severe Trauma Registry; and chest pain characteristics, electrocardiogram findings, prehospital stroke screening, and severity assessment results in the EMS Cardiovascular Registry [7–9]. All EMS run sheets and in-depth EMS registries are electronically stored at each fire department, and EMS providers can enter data using tablet devices in all regions. Dispatcher CPR registries for out-of-hospital cardiac arrest (OHCA) have been collected by dispatchers since 2012. The Smart Advanced Life Support program or the nationwide designated responses for severe disease program use independent records focused on detailed information regarding field treatment [3,4].

The EMS records are linked to external data for quality measurements. NFA and the Korea Disease Control and Prevention Agency (KCDA) constructed the Korean Out-of-Hospital Cardiac Arrest Registry (KOHCAR) in 2006. All OHCA-related EMS records are merged by the EMS Quality Committee of the NFA and sent to the KCDA. The KCDA collects hospital information and clinical outcomes through medical record reviews [10]. Since KOHCAR represents nationwide complete data collection rather than sampling, and most collected data are open to the public, KOHCAR data are used to evaluate regional and national quality improvement programs in Korea [10,11]. In 2012, NFA and KCDA started pilot projects for data collection targeting severe injury similar to KOHCAR; nationwide data collection was implemented in 2016. The Korea Severe Trauma Registry captures three target patient populations: traumatic injury, i.e., patients who met trauma center transport criteria during field triage [6]; nontraumatic injury, i.e., nontraumatically injured patients with hypotension (systolic blood pressure ≤ 90 mmHg), an abnormal respiration rate (< 10 or > 29 respirations/min), or an abnormal mental status (nonalert response according to the AVPU [alert, voice, pain, unresponsive] scale) in the field [12]; and multicasualty incidents, i.e., accidents resulting in EMS requests for six or more patients [13]. Unlike the KOHCAR, the Korea Severe Trauma Registry does not collect data on patients transported to nonemergency medical centers, and approximately 5% of patients are excluded from data collection for this reason. In addition to the two nationwide registries that collaborate with the KCDA, EMS records are also used by research consortiums, such as the Korean Cardiac Arrest Research Consortium (KoCARC) [14] or regional emergency medical service programs. Recently, the National Emergency Department Information System (NEDIS) database, which is compiled by the National Emergency Medical Center to evaluate emergency medical centers, has been linked and used for EMS quality measurement. However, because neither database contains personally identifiable information, it is difficult to link the entire dataset. Approximately 78% of all EMS transport records were linked to NEDIS data from 2017–2021. Linking the NEDIS database, which encompasses all patients who visit emergency medical centers, enables diverse EMS quality measurements beyond specific diseases.

CHALLENGES AND OPPORTUNITIES

EMS records and quality measurements have improved the Korean prehospital EMS system. However, new demands persist. First, the demand for real-time information on ambulance operation and key patient characteristics continues to increase. Since the beginning of the COVID–19 pandemic, the number of difficult cases for the selection of transfer hospitals has increased because of frequent screening or ambulance diversion from overcrowded emergency medical centers. If ambulance operating information and key patient characteristics can be accessed at the hospital level, and communication between hospitals and EMS can be strengthened, this will help solve the difficulty of selecting a transfer hospital. This strategy could also improve direct medical control, which is currently based on subjective information exchanges between personnel using cellular phones. The automatic
transfer of data collected from monitoring devices can also increase the effectiveness and efficiency of real-time data exchanges. Second, the demand for faster, easier, and wider data use is increasing, particularly among medical directors. Currently, medical directors appointed by each fire station provide feedback for EMS care; however, the scope of evaluation is limited, and feedback based on clinical diagnosis and results is difficult to obtain at this stage because only EMS records can be used. If the collection and use cycle of various data sources, including KOHCAR, Korea Severe Trauma Registry, and NEDIS databases, can be shortened and medical directors and EMS providers can more easily use these resources, more effective feedback can be achieved. The increasing demand for quality measurements in diseases beyond cardiac arrest or severe trauma emphasizes the importance of feedback linked to clinical data, as on-site screening and evaluation take precedence over field management. Further effort is required to develop a quality improvement system that allows medical directors to use data, develop quality indicators, and provide practical, authoritative feedback. Finally, the importance of acquiring patients’ medical histories in the field continues to increase. Owing to the aging population and the increase in the prevalence of underlying diseases, a patient’s medical history is an important factor for on-site management and selection of transfer hospitals. However, systematic information collection in the field is often not possible. Because each hospital uses different information and security systems, hospital data may be difficult to connect individually. However, health insurance data, which includes accumulated national data, and the National Health Insurance Service’s responsibility for managing the data, offer new possibilities for linking EMS records to hospital data. If health insurance data are summarized systematically and can be used in the field or emergency departments, the accuracy of patient evaluation and the safety of field management will be further improved. This link can also be used to calculate risk-adjusted outcomes, which can contribute to a more objective evaluation of EMS system effectiveness.

CONCLUSION

The quantitative and qualitative demands for EMS in Korea are continuously increasing. The Korean EMS is operated by the NFA through fire-based public services. Quality measurement is crucial for improving EMS systems, and various EMS records have been developed, utilized, and linked for quality measurement. The need for real-time information exchange; faster, easier, and wider utilization of databases; and the prompt acquisition of patients’ medical histories continues to increase. Strengthening communication between hospitals and EMS, improving data exchange, and linking EMS records with health insurance data can enhance the effectiveness and efficiency of EMS systems.

ETHICS STATEMENT

Not applicable.

CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

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REFERENCES


Hemodynamic management of septic shock: beyond the Surviving Sepsis Campaign guidelines

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Although the Surviving Sepsis Campaign guidelines provide standardized and generalized guidance, they are less individualized. This review focuses on recent updates in the hemodynamic management of septic shock. Monitoring and intervention for septic shock should be personalized according to the phase of shock. In the salvage phase, fluid resuscitation and vasopressors should be given to provide life-saving tissue perfusion. During the optimization phase, tissue perfusion should be optimized. In the stabilization and de-escalation phases, minimal fluid infusion and safe fluid removal should be performed, respectively, while preserving organ perfusion. There is controversy surrounding the use of restrictive versus liberal fluid strategies after initial resuscitation. Fluid administration after initial resuscitation should depend upon the patient's fluid responsiveness and requires individualized management. A number of dynamic tests have been proposed to monitor fluid responsiveness, which can help clinicians decide whether to give fluid or not. The optimal timing for the initiation of vasopressor agents is unknown. Recent data suggest that early vasopressor initiation should be considered. Inotropes can be considered in patients with decreased cardiac contractility associated with impaired tissue perfusion despite adequate volume status and arterial blood pressure. Venoarterial extracorporeal membrane oxygenation should be considered for refractory septic shock with severe cardiac systolic dysfunction.

Keywords Septic shock; Resuscitation; Fluid responsiveness; Vasopressor agent; Extracorporeal membrane oxygenation
INTRODUCTION

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Septic shock is a subset of sepsis in which underlying circulatory, cellular, and metabolic abnormalities are profound enough to substantially increase mortality [1]. Despite advances in sepsis care, sepsis remains a major cause of morbidity and mortality worldwide, including in Korea. In 2017, an estimated 48.9 million sepsis cases were recorded worldwide, and 11.0 million sepsis-related deaths were reported globally, representing 19.7% of all global deaths [2,3].

To reduce the morbidity and mortality associated with sepsis, the Surviving Sepsis Campaign (SSC) guidelines were first launched in 2002 by the European Society of Intensive Care Medicine (ESICM), the International Sepsis Forum (ISF), and the Society of Critical Care Medicine (SCCM). Since then, these guidelines have been regularly updated based on new research findings and clinical experiences [4]. While the guidelines provide standardized and generalized guidance, they are supported by evidence mainly based on randomized controlled trials (RCTs) that investigated patient response to a single intervention. However, recent large RCT studies have failed to show a difference in mortality [5-7]. The reason for this is that these RCT studies did not consider the characteristics of individual patients that may affect their response to specific interventions. Given that sepsis is a complex condition with variable clinical courses, patient phenotypes, and treatment responses, a “one-size-fits-all” management approach may not be appropriate for all patients. In this respect, the evidence-based SSC guidelines appear to be less individualized. Future sepsis treatment should be individualized based on the diversity of sepsis. This narrative review focuses on recent updates in the personalized hemodynamic management of septic shock not covered in the SSC guidelines.

PERSONALIZED HEMODYNAMIC MANAGEMENT

Hemodynamic support remains a cornerstone in the management of septic shock. Different phases exist in the management of shock, including the salvage, optimization, stabilization, and de-escalation phases [8], and monitoring and intervention should be individualized and tailored according to the phase of shock (Fig. 1) [9].

PERSONALIZED HEMODYNAMIC
MANAGEMENT

Hemodynamic monitoring and fluid management should be personalized according to the phase of shock. There is controversy surrounding the use of restrictive versus liberal fluid strategies after initial resuscitation. Fluid administration after initial resuscitation should be determined by the patient’s fluid responsiveness. Recent data suggest early initiation of vasoressors if blood pressure is not restored after initial fluid resuscitation. Venoarterial extracorporeal membrane oxygenation can be considered for refractory septic shock with severe cardiac systolic dysfunction.

Salvage phase

In the salvage phase, the goal of treatment is to provide life-saving tissue perfusion. A mean arterial pressure (MAP) of ≥ 65 mmHg and diastolic arterial pressure (DAP) of ≥ 45 mmHg should be achieved. Clinical assessment can identify patients who may respond to fluids and assess their response [10]. Altered clinical signs, including hypotension, tachycardia or bradycardia, cold extremities, skin mottling, increased capillary refill time (CRT), and oliguria, are important warning signals indicating that tissue hypoperfusion is occurring, but these signs cannot reliably indicate whether the cardiac output (CO) is low or high nor indicate the source of the hemodynamic alteration [11]. For this purpose, physicians should perform additional evaluations, such as lactate measurements and echocardiography. If cardiac impairment is suspected or the patient fails to respond to fluid therapy, bedside echocardiography is the only useful tool for rapid estimation of cardiac dysfunction along with the identification of the cause of low CO. Blood lactate level measurement is also useful for identifying impairments in tissue perfusion [9].

Optimization phase

The primary goal during the optimization phase is to optimize tissue perfusion. In addition to the monitoring tools used in the sal-
Vage phase, central venous oxygen saturation (ScvO₂) or mixed venous oxygen saturation (SvO₂) and venous-to-arterial carbon dioxide difference (Pv-aCO₂) measurement may be used to estimate tissue perfusion [9]. ScvO₂ or SvO₂ reflects the balance between the actual oxygen consumption and tissue oxygen delivery. A low ScvO₂ indicates inadequate oxygen delivery if hemoglobin and arterial oxygen saturation values are within normal ranges [9]. Pv-aCO₂, defined as the difference between the venous and arterial carbon dioxide partial pressures, is inversely related to CO. Increased Pv-aCO₂ reflects decreased microvascular blood flow during early phases of resuscitation in septic shock [12]. It is important to note that there are differences in the normalization rate between monitoring tools. In an observational study, monitoring tools such as ScvO₂, Pv-aCO₂, and CRT were already normal in > 70% of survivors at 6 hours, whereas lactate showed a much slower normalization rate, decreasing significantly at 6 hours compared to baseline but with only 52% of patients achieving normality at 24 hours [12]. Therefore, it is preferable to use several monitoring tools in combination rather than just a single one.

Transpulmonary thermodilution, an advanced monitoring tool, allows continuous and real-time monitoring of CO. It estimates the end-diastolic volume and systolic function of the four cardiac chambers. It also measures extravascular lung water (EVLW), which quantifies the volume of pulmonary edema, and pulmonary vascular permeability, which quantifies the degree of a pulmonary capillary leak [13,14]. Transpulmonary thermodilution should be considered in patients with severe septic shock.

**Stabilization phase**

In the stabilization phase, the goal is to preserve organ perfusion and prevent organ dysfunction. Cardiac dysfunction and volume overload are common in this stage, and hemodynamic tools already in use can continue to be used. In particular, repeated echocardiography may be helpful to uncover the development of right ventricular dysfunction [9].

**De-escalation phase**

Finally, in the de-escalation phase, the goal is to achieve a negative fluid balance by weaning patients off vasoactive drugs and promoting spontaneous polyuria or by inducing fluid clearance using diuretics or ultrafiltration. Monitoring can be minimized. Tissue perfusion and fluid responsiveness should be evaluated prior to fluid removal. When hypoperfusion occurs, de-escalation should be stopped [9].

**Fluid management after initial resuscitation**

For patients with sepsis-induced hypoperfusion or septic shock, the SSC guidelines suggest that ≥ 30 mL/kg of intravenous crys-
talloid fluid should be given within the first 3 hours of resuscitation [4]. This fixed volume during initial resuscitation was chosen mainly based on the results of several large RCT trials [5–7,15–17].

However, the SSC guidelines suggest no recommendation for fluid administration in patients with sepsis and septic shock who still have signs of hypoperfusion and volume depletion after initial resuscitation and that fluid resuscitation should be given only if patients present with signs of hypoperfusion. The guidelines emphasize that fluid administration after the initial fluid bolus should be guided by perfusion parameters as well as a response in hemodynamic variables [4]. Liberal fluid administration may have detrimental effects by causing edema in vital organs, leading to organ dysfunction and impairment of oxygen delivery, but the restrictive fluid strategy primarily relies on vasopressors to reverse hypotension and maintain perfusion while limiting fluid administration [18]. Observational clinical studies and randomized trials have reported harmful effects, including kidney injury, respiratory failure, or high mortality. These studies suggest that a restrictive fluid strategy is potentially superior to a liberal fluid strategy [19–23]. Recently, the results of two RCT studies related to restrictive versus liberal fluid strategies after initial resuscitation have been published. In the CLASSIC (Conservative vs. Liberal Approach to fluid therapy of Septic Shock in Intensive Care) trial [24], the restrictive fluid group received an intravenous fluids bolus of 250 to 500 mL if the patient had severe hypoperfusion, which was defined as a plasma lactate value of ≥ 4 mmol/L, a MAP of < 50 mmHg despite infusion of a vasopressor or an inotropic agent, a mottling score > 2 points (on a scale of 0–5 points, with higher scores indicating a greater area of mottling), or a urinary output of < 0.1 mL/kg/hr during the first 2 hours after randomization. In the standard fluid group, no upper limit of fluid administration was set. The study found that intravenous fluid restriction did not cause fewer deaths at 90 days than standard intravenous fluid therapy. Separately, in the CLOVERS (Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis) trial [25], patients with sepsis-induced hypotension refractory to initial treatment with 1 to 3 L of intravenous fluid were enrolled. There was no difference in 90-day mortality or adverse outcomes between groups receiving the restrictive fluid strategy (prioritizing vasopressors and lower intravenous fluid volumes) and the liberal fluid strategy (prioritizing higher volumes of intravenous fluids before vasopressor use), respectively. These studies showed that restrictive fluid therapy is not superior to liberal fluid therapy. This means that fluid administration after initial resuscitation may vary depending on the patient's fluid responsiveness and require individualized management. A comprehensive evaluation, including tissue perfusion monitoring, benefits and risks of fluid infusion, and fluid responsiveness, should be completed to achieve individualized fluid management, which should be preferred over a restrictive or liberal fluid strategy [13].

Tests to predict fluid responsiveness

The goal of fluid administration in patients with septic shock is to increase CO and tissue perfusion. However, fluid infusion can cause deleterious effects of fluid overload without an increase in CO. In an observational cohort study [26], only two-thirds of patients with septic shock were fluid-responders. Therefore, patients not responding to volume expansion may experience fluid overload [27]. Fluid overload has been shown to cause enhanced shedding of the endothelial glycocalyx, whose disruption increases vascular permeability, leading to tissue edema [28]. To prevent harmful effects of fluid overload, predicting fluid responsiveness should be the first step of a fluid strategy. Fluid responsiveness refers to a set of bedside tests that reversibly increase the preload status of the heart, allowing the clinician to assess whether this manipulation determines a significant increase in CO [29]. Fluid responsiveness is commonly defined as a stroke volume (SV) increase of ≥ 10% following a fluid bolus of 200 to 500 mL in 10 to 15 minutes [30,31]. For this purpose, static measurements of preload, including central venous pressure, inferior vena cava diameter, and arterial pressure, have been used for decades but are unreliable. Strong evidence suggests that these traditional uses should be abandoned [30–34]. In the last two decades, a number of dynamic tests have been proposed to establish and monitor fluid responsiveness (Table 1). These dynamic tests use heart-to-lung interactions, passive leg raising, or mini-fluid challenges to induce short-term changes in cardiac preloads and reveal their effects on CO [30,35]. All have some limitations, but they are frequently complementary, which helps clinicians to make the decision to give fluid or not [30,35].

In 2018, an expert statement [36] proposed an individualized fluid treatment based on a repeated bolus of 250 to 500 mL of intravenous crystalloids with the continuous monitoring of fluid responsiveness and the early administration of vasopressors if circulation fails to improve. Since it is impractical to standardize the amount of fluid according to each patient, an individualized strategy of resuscitation based on fluid responsiveness is preferable.

On the other hand, fluid unresponsiveness could be used to safely remove fluids in the hemodynamically stable patient [37].

TIMING OF VASOACTIVE AGENT INITIATION IN SEPTIC SHOCK

Septic shock results in shedding of the vascular endothelial gly-
cocalyx and endothelial damage, which leads to increased permeability, diffuse alterations in microvascular perfusion, and vasodilation due to a marked decrease in vascular tone [28]. Hypotension in patients with septic shock is known to be associated with increased mortality [37,38]. Vasoactive agents play a crucial role in septic shock management by modulating vascular tone and enhancing myocardial contractility (Fig. 2) [39]. The selection of vasoactive agents is tailored to the individual patient's hemodynamic profile and specific needs to achieve optimal cardiovascular stability and tissue perfusion. The SSC guidelines recommend nor-epinephrine as a first-line vasopressor to maintain a target MAP of 65 mmHg for initial resuscitation [4]. Norepinephrine is both an α-1 and β-1 adrenergic agonist that predominantly enhances vascular filling pressure and redistributes blood flow via its vasoconstrictive effect and myocardial contractility [40]. In septic shock patients, a decrease in norepinephrine dose led to a more significant decrease in mean systemic pressure than a decrease in resistance to venous return, leading to a reduction in venous return [41].

Timely initiation of vasopressors with fluid resuscitation is a key component in the management of septic shock. However, the optimal timing for the initiation of vasopressors has not been known. There are no recommendations on the timing of vasoactive agent initiation for septic shock treatment in the SSC guidelines. Recent data showed an association between delayed therapy and increased mortality and suggested that early initiation of vasopressors should be considered [37,42,43]. The 2018 SSC hour-1 bundle, which recommends vasopressor therapy within the first hour during or after volume resuscitation if blood pressure is not restored after initial fluid resuscitation to achieve a MAP of ≥ 65 mmHg [44]. In a retrospective study, every 1-hour delay in norepinephrine initiation during the first 6 hours after

Table 1. Tests predicting fluid responsiveness

<table>
<thead>
<tr>
<th>Test</th>
<th>Advantage</th>
<th>Limitation</th>
<th>Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPV/SVV</td>
<td>Requires no maneuver</td>
<td>Cannot be used in case of spontaneous breathing, cardiac arrhythmias, low Vt/lung compliance</td>
<td>≥ 12%</td>
</tr>
<tr>
<td>PLR</td>
<td>No fluid infusion</td>
<td>Requires a direct measurement of CO/SV</td>
<td>CO ≥ 10%</td>
</tr>
<tr>
<td>EEO test</td>
<td>Easy to perform</td>
<td>Requires a direct measurement of CO/SV</td>
<td>CO ≥ 5%</td>
</tr>
<tr>
<td>Vt challenge</td>
<td>Requires no measurement in CO/SV</td>
<td>Requires mechanical ventilation</td>
<td>PPV ≥ 1.0%–3.5%</td>
</tr>
<tr>
<td>IVC diameter variation</td>
<td>Requires no measurement in CO/SV</td>
<td>Cannot be used in spontaneous breathing, low Vt/lung compliance</td>
<td>≥ 12%</td>
</tr>
<tr>
<td>SVC diameter variation</td>
<td>Requires no measurement in CO/SV</td>
<td>Cannot be used in spontaneous breathing, low Vt/lung compliance</td>
<td>≥ 12%–36%</td>
</tr>
<tr>
<td>Mini-fluid challenge</td>
<td>Easy to perform</td>
<td>Requires a precise technique for measuring CO</td>
<td>CO ≥ 5%</td>
</tr>
<tr>
<td>Trendelenburg maneuver</td>
<td>No fluid infusion</td>
<td>Requires fluid infusion</td>
<td>VTI ≥ 10%</td>
</tr>
</tbody>
</table>

PPV, pulse pressure variation; SVV, stroke volume variation; Vt, tidal volume; PLR, passive leg raising; CO, cardiac output; SV, stroke volume; EEO, end-expiratory occlusion; IVC, inferior vena cava; SVC, superior vena cava; IAH, intra-abdominal hypertension; VT, velocity time integral; ECMO, extracorporeal membrane oxygenation.

Fig. 2. Vasoactive agents and their effects.
septic shock onset was associated with a 5.3% increase in mortality. Mortality rates at 28 days were significantly higher when norepinephrine administration was started ≥ 2 hours after septic shock onset compared to < 2 hours [42]. A very early start of vasopressors within/before the next hour of the first resuscitative fluid load was related to a significant lower net fluid balance and also with a significant reduction in the risk of death at 28 days [45].

Early high-dose vasopressor within the first 6 hours of shock is associated with lower mortality [46]. In a systematic review and meta-analysis, early initiation of norepinephrine in patients with septic shock was associated with decreased short-term mortality, a shorter time to achieve the target MAP, and a smaller volume of intravenous fluids within 6 hours [47]. In the CENSER (Early Use of Norepinephrine in Septic Shock Resuscitation) trial [48], a single-center, prospective, double-blind, placebo-controlled trial, the early vasopressor group received norepinephrine at 1.5 hours compared to 3 hours in the standard treatment group. The shock control rate at 6 hours, which was the primary endpoint, was met in 76.1% of patients in the early vasopressor group compared to 48.4% of patients in the standard group (P < 0.001), while there was no difference in 28-day mortality between these groups.

In contrast, earlier vasopressor use with a restrictive fluid strategy compared to later vasopressor use with a liberal fluid strategy did not result in significantly lower (or higher) mortality before discharge home by day 90 [25]. Similarly, vasopressor initiation within 1 hour of fluid loading was associated with higher 28-day mortality in patients with septic shock [49].

DAP and the diastolic shock index (DSI), defined as the ratio between heart rate and DAP, may be used to guide the timing of vasopressor initiation in septic shock. It seems logical to initiate vasopressors when DAP < 45 mmHg or DSI > 2, which indicates severe vasodilation [50]. A retrospective observational study showed that in patients with high DSI (≥ 2.0) and high lactate levels (≥ 2.5 mmol/L), early initiation of vasopressor therapy was associated with decreased 28-day mortality [51]. These data suggest that norepinephrine should be initiated early, ideally within 1 hour of shock onset, but after adequate fluid resuscitation. DSI and lactate measurement can help guide the appropriate time to initiate vasopressor therapy in septic shock [52].

The SSC guidelines suggest adding vasopressin instead of escalating the dose of norepinephrine in adults with septic shock on norepinephrine with inadequate MAP levels. However, the timing of vasopressin initiation is not well-described in the literature. In VASST (Vasopressin and Septic Shock Trial) [53], there was no difference in 28-day mortality, but subgroup analyses identified a mortality benefit with the use of vasopressin in patients with less severe septic shock, i.e., those with a norepinephrine dose at randomization of ≤ 15 μg/min and those with a lactate concentration at randomization of ≤ 1.4 mmol/L. In a retrospective, observational study, a greater norepinephrine-equivalent dose at vasopressin initiation and a higher lactate concentration at vasopressin initiation were each associated with higher in-hospital mortality in patients with septic shock [54]. These data indicate that vasopressin should be initiated when patients are on low norepinephrine-equivalent doses or have low lactate concentrations. While the SSC guidelines suggest vasopressin initiation when the norepinephrine dose is in the range of 0.25 to 0.5 μg/kg/min [4], vasopressin initiation may be considered before norepinephrine-equivalent doses exceed 0.1 to 0.2 μg/kg/min (10–15 μg/min) [52].

Epinephrine should be considered as a third-line treatment for septic shock, and its use should be limited to those patients with inadequate MAP levels despite norepinephrine and vasopressin administration [4]. The specific norepinephrine-equivalent dose at which epinephrine should be administered in septic shock is unknown. One study [55] identified the optimal norepinephrine-equivalent dose range for initiating epinephrine as 37 to 133 μg/min. In this dose range, 29% of patients achieved hemodynamic stability with the initiation of epinephrine, while 15% of patients who had epinephrine initiated outside of this dose range achieved hemodynamic stability (P = 0.03).

INOTROPES

Sepsis-induced cardiomyopathy (SCM) is a reversible myocardial dysfunction caused by sepsis. The prevalence of SCM varies from 10% to 70%, although studies defining SCM as an ejection fraction of < 45% have generally reported a prevalence of 30% to 50% [56]. Inotropes can be considered in patients with decreased cardiac contractility associated with impaired tissue perfusion. The SSC guidelines suggest either adding dobutamine to norepinephrine or administering epinephrine alone for adults with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate volume status and arterial blood pressure [4]. Adverse effects (tachyarrhythmia, increased heart rate, hypertension, and myocardial oxygen consumption) and specific risks (hypertrophic cardiomyopathy, myocardial ischemia) should be carefully investigated, and the risk/benefit profile of intervention should be evaluated [9]. Milrinone is a phosphodiesterase inhibitor that increases intracellular cyclic adenosine monophosphate, leading to inotropic effects independent of β-adrenergic receptors [15]. Milrinone may be an effective therapeutic in patients recently on β-blockers [57]. Experts suggest adopting a stepwise approach to
administering inotropics, as follows. First, begin with a limited dose of dobutamine (2.5–5.0 μg/kg/min) and evaluate efficacy and tolerance. If there is still severe contractility impairment, higher doses (≤ 20 μg/kg/min) may be considered. Second, substitute or add enoximone or milrinone and evaluate the efficacy and tolerance. Third, substitute or add levosimendan in cases of severe impairment. At each step, improvements in cardiac function and CO as well as resolution of tissue hypoperfusion and tolerance (e.g., lack of tachycardia, arrhythmias, etc.) should be evaluated. As soon as the situation improves, weaning off inotropics should be attempted [9]. However, the SSC guidelines suggest against using levosimendan, as it was not superior to dobutamine in adults with sepsis in terms of mortality [4,58].

TIMING OF CORTICOSTEROID INITIATION IN SEPTIC SHOCK

Sepsis results in disruption of the hypothalamic-pituitary-adrenal axis, which may translate into cardiovascular and other organ dysfunction and eventually an increased risk of death. Corticosteroids are known to improve cardiovascular function via sodium and water retention, restore systemic vascular resistance, and decrease organ failure [59]. Three recent large RCTs [60–62] showed that corticosteroids accelerate the resolution of shock, but there was no clear effect on short- or long-term mortality. The SSC guidelines suggest administering intravenous corticosteroids in patients with septic shock and ongoing requirements for vasopressor therapy [4].

Although there is no clear recommendation with regard to the time of initiation of corticosteroids in septic shock patients, the early initiation of corticosteroid therapy in sepsis, specifically within 24 hours of shock, despite adequate fluid resuscitation and vasopressor administration (norepinephrine-equivalent dose of 0.5–1 μg/kg/min) is reasonable [52]. A retrospective cohort study reported decreased intensive care unit mortality when hydrocortisone was administered within 0 to 6 hours after shock onset compared to > 48 hours after shock onset (odds ratio, 0.6; 95% confidence interval 0.4–0.8) and suggested that hydrocortisone should be started within the first 12 hours after shock onset [63].

A recent multicenter, propensity score-weighted observational cohort study (n = 198) [64] evaluated early (≤ 12 hours of vasopressor initiation) versus late (> 12 hours of vasopressor initiation) low-dose corticosteroid initiation in septic shock and determined that early initiation was associated with a shorter time to vasopressor discontinuation (40.7 hours vs. 60.6 hours, P = 0.0002). The SSC guidelines suggest that corticosteroid administration is commenced ≥ 4 hours after vasopressor initiation and at norepinephrine or epinephrine doses of ≥ 0.25 μg/kg/min [4].

VA ECMO IN SEPTIC SHOCK

While the SSC guidelines suggest using venovenous extracorporeal membrane oxygenation (ECMO) when conventional mechanical ventilation fails for sepsis-induced severe acute respiratory distress syndrome, there is no suggestion of deploying venoarterial (VA) ECMO in septic shock complicated by SCM [4]. Most early studies of VA ECMO for refractory septic shock complicated by SCM reported low survival rates and poor outcomes [65]. A recent retrospective, multicenter study [66] showed that patients with severe sepsis-induced cardiogenic shock treated with VA ECMO experienced a large and significant improvement in survival compared to controls not receiving ECMO (60% vs. 25%, P < 0.0001). A meta-analysis of 468 patients placed on VA ECMO for refractory septic shock [67] reported an overall survival rate of 36% and a significantly higher survival rate among patients with ejection fractions of < 20% compared to those with ejection fractions of > 35% (62% vs. 32.1%, P = 0.05). Therefore, VA ECMO should be considered as a bridge therapy to recovery for patients with refractory septic shock with severe cardiac systolic dysfunction and end-organ hypoperfusion. However, VA ECMO should not be used to manage patients with isolated vasodilatory septic shock without significant myocardial dysfunction [65].

CONCLUSION

Sepsis is a complex condition with variable clinical courses, patient phenotypes, and treatment responses. Personalized hemodynamic monitoring and fluid responsiveness based on the phase of septic shock are essential in septic shock management to assess the patient’s cardiovascular status, guide fluid resuscitation, determine the need and timing for vasopressors and inotropic agents, and optimize tissue perfusion, which leads to improved outcomes in septic shock.

ETHICS STATEMENT

Not applicable.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.
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shock index and clinical outcomes in patients with septic


Benefits, key protocol components, and considerations for successful implementation of extracorporeal cardiopulmonary resuscitation: a review of the recent literature

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The application of venoarterial extracorporeal membrane oxygenation (ECMO) in patients unresponsive to conventional cardiopulmonary resuscitation (CPR) has significantly increased in recent years. To date, three published randomized trials have investigated the use of extracorporeal CPR (ECPR) in adults with refractory out-of-hospital cardiac arrest. Although these trials reported inconsistent results, they suggest that ECPR may have a significant survival benefit over conventional CPR in selected patients only when performed with strict protocol adherence in experienced emergency medical services–hospital systems. Several studies suggest that identifying suitable ECPR candidates and reducing the time from cardiac arrest to ECMO initiation are key to successful outcomes. Prehospital ECPR or the rendezvous approach may allow more patients to receive ECPR within acceptable timeframes than ECPR initiation on arrival at a capable hospital. ECPR is only one part of the system of care for resuscitation of cardiac arrest victims. Optimizing the chain of survival is critical to improving outcomes of patients receiving ECPR. Further studies are needed to find the optimal strategy for the use of ECPR.

Keywords Heart arrest; Cardiopulmonary resuscitation; Extracorporeal membrane oxygenation

Capsule Summary

What is already known
The use of extracorporeal cardiopulmonary resuscitation (ECPR) has significantly increased in recent years. Current resuscitation guidelines recommend its use as a rescue method in selected patients with refractory cardiac arrest.

What is new in the current study
Despite the increased use of ECPR, its clinical efficacy, suitable patient population, and optimal implementation strategy remain unclear. ECPR may have a significant survival benefit over conventional CPR in selected patients only when performed in an experienced system and strictly following protocol. Optimizing the chain of survival is critical to improving outcomes of patients receiving ECPR.
INTRODUCTION

Cardiac arrest is a major cause of mortality worldwide, affecting 500,000 people annually in the United States alone [1–5]. In Korea, approximately 30,000 patients with cardiac arrest are treated using emergency medical services (EMS) each year [6]. Chances of survival after cardiac arrest decrease rapidly as the duration of cardiopulmonary resuscitation (CPR) increases [7–9]. Outcomes of patients’ refractory to initial resuscitation efforts are highly unfavorable [10,11].

The application of venoarterial extracorporeal membrane oxygenation (ECMO) in patients unresponsive to conventional CPR (commonly referred to as extracorporeal CPR [ECPR]) has significantly increased in recent years [12]. Cardiac output generated during conventional CPR is insufficient to maintain vital organ perfusion [13,14], and hypoxic-ischemic injury risk increases until the return of spontaneous circulation (ROSC). ECMO effectively restores vital organ perfusion, facilitating ROSC and buying time to identify and treat the underlying cause of cardiac arrest. Despite its increased use, the clinical efficacy of and the patient population most suitable for ECPR remain unclear. Although current resuscitation guidelines recommend ECPR as a rescue method in refractory cardiac arrest [15], a standard protocol for ECPR is lacking.

Here, we provide insights regarding the optimal implementation of ECPR based on a review of recent evidence on the clinical efficacy of ECPR and a summary of recent research on the key components of ECPR protocols and considerations for incorporating ECPR within a system of care.

IS ECPR MORE EFFECTIVE THAN CONVENTIONAL CPR?

A number of studies have investigated the relationships between ECPR and outcomes in patients with refractory cardiac arrest [16–19]. Although these studies report inconsistent results, several studies reported significant associations between ECPR use and positive outcomes [17,18]. To date, three published randomized trials have investigated ECPR use in adult patients with refractory cardiac arrest (Table 1) [20–22]. The first is the ARREST (Advanced Reperfusion Strategies for Refractory Cardiac Arrest) trial [20], which included adult patients with refractory ventricular fibrillation out-of-hospital cardiac arrest (OHCA) who had estimated transfer times to the University of Minnesota medical center of less than 30 minutes. The patients were randomized to either ECMO-facilitated resuscitation or standard advanced cardiovascular life support (ACLS) on arrival at the catheterization lab. The ARREST trial showed a significantly higher rate of survival to hospital discharge in the ECMO group compared to the standard ACLS group (43% vs. 7%) in the interim preplanned analysis after enrolling 30 patients, leading to premature termination of the trial because of the apparent survival benefit of ECMO-facilitated resuscitation.

The Prague OHCA study [21] was a single-center trial conducted in Prague, Czech Republic, which included 256 adult patients with refractory OHCA of presumed cardiac origin randomized during on-scene CPR to either an invasive strategy including prompt intra-arrest transport to a cardiac center under mechanical CPR, in-hospital ECPR, and immediate invasive assessment and treat-

Table 1. Overview of published randomized trials investigating ECPR in adult patients with refractory OHCA

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>No. of patients</th>
<th>Location</th>
<th>Group assignment</th>
<th>Witnessed arrest</th>
<th>Bystander CPR</th>
<th>Shockable rhythm</th>
<th>Time to ECMO initiation (min)</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARREST trial [20]</td>
<td>Single-center RCT</td>
<td>30</td>
<td>USA</td>
<td>After hospital arrival</td>
<td>24 (80.0)</td>
<td>25 (83.3)</td>
<td>30 (100)</td>
<td>Present</td>
<td>59 ± 28</td>
</tr>
<tr>
<td>Prague OHCA study [21]</td>
<td>Single-center RCT</td>
<td>256</td>
<td>Czech Republic</td>
<td>During prehospital CPR</td>
<td>256 (100)</td>
<td>252 (98.4)</td>
<td>156 (60.9)</td>
<td>Present</td>
<td>61 (55–70)</td>
</tr>
<tr>
<td>INCEPTION trial [22]</td>
<td>Multicenter RCT</td>
<td>134</td>
<td>Netherlands</td>
<td>During intra-arrest transport</td>
<td>131 (97.8)</td>
<td>130 (97.0)</td>
<td>132 (98.5)</td>
<td>Absent</td>
<td>74 (63–87)</td>
</tr>
</tbody>
</table>

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

ECPR, extracorporeal cardiopulmonary resuscitation; OHCA, out-of-hospital cardiac arrest; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; ARREST, Advanced Reperfusion Strategies for Refractory Cardiac Arrest; RCT, randomized clinical trial; ACLS, advanced cardiovascular life support; INCEPTION, Early Initiation of Extracorporeal Life Support in Refractory Out-of-Hospital Cardiac Arrest.
ment (n = 124) or to the standard strategy (continued on-scene ACLS, n = 132). In the study, the primary outcome was survival with a good neurologic outcome at 180 days, which was comparable between groups (31.5% vs. 22.0% for the invasive and standard strategies, respectively; P = 0.09) in the intention-to-treat analysis, and the study was terminated based on a prespecified stopping rule for futility. However, in the Prague OHCA study, 66% of the invasive strategy group underwent ECPR compared to 8% of the standard strategy group. The crossovers could have affected the results of the intention-to-treat analysis. A secondary analysis of the Prague OHCA study revealed that the use of ECPR was significantly associated with 180-day survival in patients without prehospital ROSC [23]. Although both trials were terminated before enrolling the originally planned number of patients, both favored ECPR over conventional CPR. A meta-analysis by Scquizzato et al. [24] that included the two randomized trials and four propensity score–matched studies showed significant benefit of ECPR over conventional CPR with regard to survival with good neurologic outcomes.

The INCEPTION (Early Initiation of Extracorporeal Life Support in Refractory Out-of-Hospital Cardiac Arrest) trial [22] is the most recent randomized trial and involved 10 cardiosurgical centers served by 12 EMS agencies in the Netherlands. In this trial, 134 adult patients with witnessed refractory OHCA with initial shockable rhythm randomly received ECPR (n = 70) or conventional CPR (n = 64) at one of the participating centers. The authors found no significant between-group difference in 30-day survival with good neurologic outcomes (20% vs. 16% in the ECPR and conventional CPR groups, respectively; P = 0.52).

In view of the inconsistent findings from the three randomized trials, whether ECPR can yield better outcomes than conventional CPR in patients with refractory OHCA remains unclear. However, considering that all three trials showed numerically higher survival rates for the ECPR groups, these trials may have been underpowered to detect any survival benefit that was present.

These three trials also had considerable differences in patient selection, trial setting, and EMS treatment strategy. The ARREST trial included only patients with shockable rhythms, randomized patients to treatment on arrival to the catheterization lab, and was performed at an experienced, high-volume center with a specific protocol. In contrast, 39.1% of patients in the Prague OHCA study presented with nonshockable rhythms. The randomization was performed during on-scene CPR, and thus patients assigned to the standard strategy group received continued on-scene resuscitation. The INCEPTION trial was performed at multiple centers with relatively low case volumes without a standardized ECPR protocol. The characteristics of the Prague OHCA study and INCEPTION trial could have contributed to the lower survival rates of ECPR groups and higher survival rates of conventional treatment groups in these trials compared to those in the ARREST trial, ultimately leading to the lack of significant survival benefit of ECPR seen in these two trials. Results of these trials suggest that ECPR may have a significant survival benefit over conventional CPR in selected patients only when performed in an experienced system with strict protocol adherence.

Given the greater accessibility to ECMO in in-hospital settings than out-of-hospital settings, patients with in-hospital cardiac arrest (IHCA) are likely better candidates for ECPR than those with OHCA. Although several observational studies have suggested survival benefits of ECPR in IHCA [7,25], results of randomized trials evaluating the effectiveness of ECPR in IHCA are currently lacking. Further studies are required to resolve the existing uncertainty over the benefits of ECPR.

**KEY COMPONENTS OF THE ECPR PROTOCOL**

The complete ECPR process must be well-defined through a rapidly deployable protocol to enable timely initiation of ECMO. ECPR outcomes in the absence of a well-defined ECPR protocol can be highly unfavorable [26–28]. Various protocols with differing candidate selection criteria, and cannulation and postcannulation managements are used for ECPR [29], none of which have been widely accepted.

**Candidate selection**

Clearly defined candidate selection criteria in an ECPR protocol would allow rapid recognition of potential candidates for ECPR. A variety of candidate selection criteria have been used in ECPR protocols [29,30]. Most are based on cardiac arrest–related factors known to be associated with outcomes of patients undergoing conventional CPR. Several factors, including witnessed arrest, presenting rhythm, and CPR duration, have been associated with outcomes after ECPR (Fig. 1) [23,31–37].

Advanced age has been included as an exclusion criterion in many protocols [29], although the cutoffs vary widely. Some studies reported significant associations between advanced age and poor outcomes in patients undergoing ECPR [38–41]; however, other studies reported no associations between advanced age and poor outcomes [32,33]. A recent study suggested that a significant number of elderly patients (> 75 years) survive with good neurologic outcomes after ECPR [42]. ECPR should therefore not be excluded from treatment options based only on advanced age.

Initial electrocardiogram rhythm has frequently been used as an inclusion or exclusion criterion [29]. Several studies have shown...
significant associations between shockable rhythms and good outcomes in patients undergoing ECPR [31–36,43,44]. The survival rate in the invasive strategy group in the Prague OHCA study (31.5%) was lower than that in the ARREST trial (43.0%) that included only patients with initial shockable rhythms [20,21]. In the Prague OHCA study, the survival rate of patients with initial shockable rhythms in the invasive strategy group (48.6%) was close to that in the ARREST trial. In a post hoc analysis of the Prague OHCA study [43], initial shockable rhythm was significantly associated with neurologically favorable survival. Considering the results of these studies [20,21,31–36,43,44], only selecting patients with an initial shockable rhythm would improve outcomes after ECPR. Although patients with initial nonshockable rhythms have worse prognosis than those with initial shockable rhythms, patients with refractory cardiac arrest should not be excluded from ECPR only because of initial nonshockable rhythms. Several studies suggest that ECPR yields favorable outcomes in patients with initial nonshockable rhythms in the presence of other findings indicating likely good neurologic recovery (i.e., witnessed arrest, bystander CPR, and signs of life) [45,46]. In addition, a recent study reported that ECPR was associated with increased survival among patients whose electrocardiogram rhythm was initially nonshockable but later converted to a shockable rhythm [47].

The duration of CPR until ECPR initiation is a key determinant of outcomes after ECPR administration. Multiple studies suggest significant associations between prolonged CPR duration and poor outcomes after ECPR administration [36,48–50]. Defining refractory cardiac arrest with a shorter CPR duration in a protocol would lead to improved ECPR outcomes. Lamhaut et al. [26] reported an increase in survival from 8% to 29% after reducing the CPR duration for patient selection from 30 to 20 minutes. However, a shorter CPR duration may increase the risk of unnecessary exposure of patients who would survive with conventional CPR alone to ECMO. Although the maximal CPR duration beyond which ECPR becomes futile remains uncertain, 60 minutes is the most frequently used maximum allowable CPR duration [29]. Several studies suggest that the time to ECMO initiation of ≤ 60 minutes is associated with better outcomes [51,52]. The current Extracorporeal Life Support Organization (ELSO) guidelines also recommend commencing ECMO support within 60 minutes after cardiac arrest [53]. The time required to initiate ECMO support after the decision to apply ECPR may vary between institutions depending on the infrastructure and capabilities of the cannulation team. The mean time from catheterization lab arrival to ECMO initiation in the ARREST trial was 7 minutes [20], whereas the median time required for cannulation in the INCEPTION trial was 20 minutes [22]. Therefore, it is reasonable to set a maximal CPR duration in ECPR protocols, taking the time required for cannulation in each setting into account, with the goal of initiating ECMO within 60 minutes after cardiac arrest.

Clinical characteristics such as gasping, body movements, and reactive pupils, commonly referred to as signs of life, can help identify ECPR candidates. Signs of life have been associated with good outcomes after ECPR [54]. Several studies suggested that initial laboratory markers, including pH and lactate levels, can also identify favorable candidates for ECPR [34,55–57]. These laboratory markers are objective but not always available before ECPR implementation.

Several scoring systems have been proposed to assist in candidate selection for ECPR [58]. The TiPS65 score was developed using data from adult patients with shockable OHCA treated with ECPR in Japan. It is calculated by adding points from four variables: time from call to hospital arrival ≤ 25 minutes (Tt), pH ≥ 7.0 (P), shockable rhythm (S), and age < 65 years (65). Validation studies of the TiPS65 score showed a C-statistic of 0.729 (95% confidence interval, 0.672–0.786) for prediction of 30-day survival with good neurologic outcomes [59]. The RESCUE–IHCA (Resuscitation Using CPR During IHCA) score was developed using data from adult patients with IHCA treated with ECPR from Get With The Guidelines–Resuscitation (GWTG-R) [60]. This score considers six variables (age, preexisting renal insufficiency, time of day, illness category, presenting rhythm, and duration of cardiac arrest) and shows fair discriminatory (area under the curve, 0.676; 95% confidence interval, 0.606–0.746) and good calibration performances in a validation cohort from the ELSO registry. Clinical utility of these scoring systems remains to be determined.

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**Fig. 1.** Favorable and unfavorable factors for extracorporeal cardiopulmonary resuscitation (ECPR).
Several studies have suggested that strict candidate selection criteria may improve ECPR outcomes [26,30,61–63]. A systematic review that assessed the effects of predefined selection criteria on survival after ECPR showed that an increased number of inclusion criteria was associated with improved outcomes in prospective studies [30]. However, using stricter criteria results in identifying fewer eligible patients, thereby increasing the risk of excluding potential candidates from receiving ECPR. Further studies are needed to determine candidate selection criteria that can maximize the benefits of ECPR while minimizing futile ECMO initiation.

Implementing ECPR

ECPR involves a series of time-critical interventions. Detailed information on the procedures, materials, and equipment necessary for ECPR (Fig. 2), should be included in ECPR protocols. Using pre-primed ECMO circuits can reduce the time to ECMO initiation. Several studies reported that sterility of preprimed ECMO circuits remained uncompromised for more than 1 month [64,65]. Ultrasoundography plays an important role in ECMO cannulation by localizing the femoral vessels and providing real-time imaging during cannulation (Fig. 3), leading to faster ECMO cannulation [66].

The percutaneous Seldinger or surgical cutdown techniques are the most commonly used for inserting the ECMO cannula into the common femoral artery and vein. Although the percutaneous Seldinger technique is more frequently used [29], it often fails even with ultrasonographic guidance [67]. The surgical technique is mostly used as a salvage measure after failed percutaneous access attempts and is associated with higher risk of local infection [68]. Which technique is better between the two remains unestablished, and the first choice of technique may depend on the operator’s preference and the patient’s anatomic characteristics. Chen et al. [67] reported that arterial diameter was significantly associated with the success of percutaneous ECMO cannulation using the Seldinger technique, with an arterial diameter of > 4.5 mm yielding a relatively high success rate.

Because inadvertent venous placement of the arterial cannula can impede timely ECMO initiation, procedures to differentiate between arterial and venous puncture must be included in ECPR protocols. The color of blood taken at the puncture site can help in differentiating between arterial and venous puncture before guidewire insertion [69]. A guidewire-induced hyperechoic shadow within the inferior vena cava on ultrasonography confirms venous puncture (Fig. 4). Even after successful guidewire insertion, complications such as guidewire kinking or vessel perforation can occur during sequential dilations or cannula advancement. Moving the guidewire back and forth during sequential di-

### List of materials and equipment needed to perform ECPR

| Preoperative skin preparation (e.g., chlorhexidine, povidone-iodine, and isopropyl alcohol) |
| Surgical drape, gown, and gloves |
| Vascular ultrasound probe |
| Sterile ultrasound probe cover |
| Peripheral IV catheters (18–24 gauge) |
| Invasive pressure transducer kit |
| Arterial pressure monitor |
| Pressure infusion bag |
| Normal saline IV bags |
| Heparin |
| Tubing clamps |
| Surgical instruments |
| Syringes (10 and 50 mL) |
| Three-way stopcocks |
| Rubber tubing |
| Kidney basin |
| Surgical suture |
| Percutaneous ECMO insertion kit |
| Arterial and venous ECMO cannulas |
| ECMO pump device with primed oxygenator circuit |

Fig. 2. An example of a list of materials and equipment needed to perform extracorporeal cardiopulmonary resuscitation (ECPR). IV, intravenous; ECMO, extracorporeal membrane oxygenation.

Fig. 3. Transverse view of the common femoral artery and vein. Arrows point to shadow artifact of needle entering the femoral artery. (A) The needle tip is in the muscle layer above the common femoral artery (CFA). (B) The needle tip is about to enter the CFA. CFV, common femoral vein.
lations and cannula advancement may help reduce complications. Upon sensing resistance to guidewire movement, advancement of the dilator or cannula should be stopped. When an arterial catheter is placed at the time of ECMO initiation, observing the arterial pressure waveform may also help in detecting cannula misplacement. Cannula misplacement should be suspected if there is no gradual increase in arterial pressure immediately after ECMO initiation (Fig. 5).

ECMO should be initiated as soon as possible after the decision to apply ECPR is made. Placing angiocatheters in the femoral artery and vein during the initial assessment for ECPR candidacy and replacing the angiocatheters with ECMO cannulas after the decision to apply ECPR is made, rather than initiating ECMO cannulation after the decision, may help reduce the time taken to initiate ECMO [70]. High-quality CPR should be provided throughout the resuscitation until ECMO support is initiated. Multiple studies have reported no survival benefit of mechanical CPR over manual CPR [71,72]. However, the use of a mechanical CPR device may enable provisioning high-quality CPR until initiation of ECMO support and more space around the patient for ECMO cannulation, thus facilitating successful ECPR implementation.

Post-ECMO implementation care
Management after ECMO implementation should be part of ECPR protocols to ensure a highly protocolized sequence of care for patients, including diagnosis and treatment of arrest cause, hemodynamic and oxygenation support, monitoring and management of ECMO-related complications, and neuroprognostication. Several studies suggest a significant association between post-ECMO implementation care and good outcomes in patients undergoing ECPR [73,74].

Promptly diagnosing and treating the arrest cause after ECMO initiation can maximize chances of recovery. Patients with refractory cardiac arrest have a high prevalence of coronary artery disease (70%–80%) [75,76]. Therefore, emergent coronary angiography should be included in the ECPR protocol. Current ELSO guidelines recommend emergent coronary angiography for all patients undergoing ECPR without an obvious noncardiac etiology of arrest [53]. Multiple studies suggest a significant association between coronary angiography and/or percutaneous coronary intervention with improved outcomes in patients undergoing ECPR [36,73,77].

Current ELSO guidelines recommend routine computed tomography (CT) imaging of the brain, chest, and abdomen/pelvis as soon as possible in all ECPR cases [53]. Head CT helps in identifying in-

Fig. 4. Ultrasonographic image showing guidewire-induced hyperechoic shadow (arrow) within the inferior vena cava.

Fig. 5. Screenshots of patient monitor (A) before and (B) immediately after extracorporeal membrane oxygenation (ECMO) initiation. Green, red, and white lines indicate electrocardiographic, arterial pressure, and right atrial pressure data, respectively. Note the progressive increase in the arterial pressure immediately after ECMO initiation.
tracranial hemorrhage, a common cause of cardiac arrest [78], and in predicting neurologic outcomes [78,79]. CT of the chest and abdomen/pelvis helps elucidate the cause of cardiac arrest, such as pulmonary embolism, and complications from prolonged CPR or ECMO cannulation. Several studies indicate the utility of whole-body CT after ECPR [80–82]. Ososky et al. [82] evaluated the utility of whole-body CT in detecting clinically significant findings in 38 patients who underwent ECPR and whole-body CT. They reported that whole-body CT detected clinically significant findings in 37 patients (97%) and led to subsequent interventions in 20 patients (54%). ECMO poses unique technical challenges to contrast-enhanced CT imaging. For example, a significant volume of contrast material administered intravenously can be aspirated into the venous cannula and returned to the aorta via the arterial cannula, bypassing the pulmonary artery. ECMO flow needs to be temporarily reduced or stopped after contrast material administration to obtain images of sufficient quality to diagnose pulmonary embolism.

Treatment-refractory shock is the most common cause of death after ECPR [83]. Hemodynamic monitoring in patients receiving ECMO is challenging. Hemodynamic measurements using thermodilution techniques and those based on pulse contour analysis algorithms are unreliable during ECMO. An arterial line should be placed immediately (preferably in the right radial artery). Several studies reported significant associations between mean arterial pressure (MAP) and outcomes in patients resuscitated with ECPR [35,49,84,85]. In an observational study including 253 adult patients resuscitated with ECPR [49], patients with MAP of approximately 75 mmHg had the lowest probability of poor neurologic outcomes. Setting the MAP target to 60–80 mmHg according to the ELSO guidelines would be reasonable [53]. The optimal ECMO flow target in the early post-ECMO implementation period is unknown. The ECMO flow rate can be adjusted by referring to the method used in the ARREST trial [86]. In the ARREST trial, ECMO flow was maximized until vasopressors were discontinued and then decreased as tolerated to promote native cardiac function [86]. Pulse pressure on arterial pressure waveform is dependent on cardiac contractility and afterload and can be used to monitor hemodynamic state in patients undergoing vena-arterial ECMO. A low pulse pressure has been associated with unsuccessful weaning from ECMO support and in-hospital mortality in patients undergoing ECPR [87,88]. Loss of pulse pressure indicates a predominance of blood flow through the ECMO circuit, with negligible blood flow through the native heart, which can cause left ventricular dilation. Left ventricular dilation can in turn cause pulmonary edema and myocardial injury, impeding cardiac recovery. Echocardiographic assessment of left ventricular dimensions and function and aortic valve opening help in diagnosing this complication. Several studies suggest a significant association between the use of mechanical left ventricular unloading and improved survival in patients undergoing ECPR [73,89]. ECPR protocols should include diagnostic and therapeutic options that can be used when pulse pressure is lost (e.g., inotropic support, afterload reduction, and intra-aortic balloon pump).

Upon ECMO initiation, sweep gas containing 100% oxygen is typically delivered at a flow rate matching the ECMO flow, frequently leading to hyperoxemia and hypocarbica. Pulmonary complications including pulmonary edema and acute respiratory distress syndrome frequently occur in patients with cardiac arrest [90,91]. Patients with impaired pulmonary gas exchange can be exposed to hypoxemia despite ECMO support because of a phenomenon known as Harlequin syndrome (difference in cerebral and lower extremity oxygenation due to hypoxic blood from the native heart flowing to the brain and hyperoxic blood from the ECMO circuit flowing to the lower extremities). Multiple studies reported significant associations between arterial blood gas derangement and poor outcomes in patients undergoing ECPR [73,92–95]. In a retrospective study including 3,125 patients that received ECPR [92], severe hyperoxemia (≥ 300 mmHg) was associated with ischemic stroke, intracranial hemorrhage, and in-hospital mortality. Given the associations between arterial blood gas derangement and poor outcomes [92–96], frequent evaluation of arterial blood gases and careful titration of the ECMO gas blender setting are required to avoid arterial blood gas derangement that can adversely affect outcomes.

Whether targeted temperature management (TTM) improves outcomes of patients receiving ECPR remains unknown. Observational studies have yielded inconsistent results [36,97–99]. Randomized trials evaluating the effects of TTM on outcomes of patients treated with ECPR are lacking. However, given the high incidence of hypoxic-ischemic brain injury in patients undergoing ECPR [100], TTM can be reasonably considered for patients who remain comatose after ECPR. The ELSO guidelines recommend application of TTM targeting 33 to 36 °C for 24 hours to comatose patients after ECPR according to protocols that yielded excellent results [53,76,101].

ECMO is a highly invasive intervention with a high risk of complications [102,103]. Bleeding is a common complication and usually occurs at the cannulation site [104]. In the Prague OHCA study [21], bleeding was twice as common in the invasive strategy group (31%) than in the standard strategy group (15%). Cannulation site bleeding is usually controlled with manual pressure and rarely requires surgery [23,67]. Uncontrollable or serious bleeding within the central nervous system, thoracic cavity, or gastrointestinal tract, although uncommon, has been reported in patients under-
going ECPR [101,105]. In a study that investigated the effect of bleeding and red blood cell transfusion during ECMO on mortality [106], the volume of red blood cells transfused was significantly associated with in-hospital mortality. Screening measures for early detection of bleeding complications (e.g., complete blood count and ultrasonography) should be included in ECPR protocols.

Although anticoagulation strategies vary among ECMO protocols, anticoagulation is typically provided by an initial intravenous bolus of unfractionated heparin (5,000 units) followed by a continuous infusion titrated to maintain an activated clotting time (ACT) of 180 to 220 seconds or a partial thromboplastin time of 1.5 times the upper normal limit. Patients undergoing ECPR are prone to coagulation disorders, such as prolonged prothrombin time and partial thromboplastin time with thrombocytopenia [107, 108], which may reduce anticoagulant requirements. Several studies suggest that avoiding the initial bolus dose or targeting low ACT levels may be helpful [109–111]. In a meta-analysis that evaluated the effect of different anticoagulant methods on bleeding/thromboembolic complications in patients receiving ECMO [111], the incidence of bleeding events and of thromboembolic events were higher among those who received an initial heparin loading dose than those who did not. In comparisons among the three different ACT level groups, the incidences of both bleeding and thromboembolic events were the highest in the high ACT group.

Further studies are needed to confirm the safety and efficacy of the reduced anticoagulation strategy.

Limb ischemia distal to the arterial cannula site is a common complication of peripheral venoarterial ECMO, with an incidence of 10% to 20% [67,82,112]. A larger cannula size, diabetes, and CPR duration have been suggested as risk factors for distal limb ischemia [67,113]. Placing a distal limb perfusion cannula is recommended to prevent distal limb ischemia [53]. Distal limb perfusion cannula placement may not only decrease the risk of distal limb ischemia, but also improve survival in patients undergoing ECPR [73,114]. In a study including 7,488 adult patients treated with ECPR [73], placement of a distal limb perfusion cannula was independently associated with improved survival. Distal limb ischemia can still occur despite distal limb perfusion through the cannula [114]. Regular monitoring of distal limb perfusion should be included in ECPR protocols. Current ELSO guidelines suggest near-infrared spectroscopy for monitoring distal limb perfusion [53]. Several studies have suggested that monitoring calf tissue oxygen saturation using near-infrared spectroscopy may be useful for detecting distal limb ischemia [115,116].

According to current resuscitation guidelines [15], multimodal neuroprognostication should be performed at least 72 hours after achieving normothermia. Although whether the same approach reliably predicts neurologic outcomes in patients resuscitated with ECPR remains to be established, several studies have suggested that prognostic measures used for patients experiencing cardiac arrest not treated with ECMO may also be applicable to patients resuscitated with ECPR [117–119]. Ben-Hamouda et al. [117] compared the performance of prognostic measures, including pupillary reflex, electroencephalogram, somatosensory evoked potentials, and neuron specific enolase, between comatose cardiac arrest survivors treated with and without ECMO and reported comparable performances between both groups. Further studies are needed to identify the optimal neuroprognostication method in the ECPR population.

**APPROACHES OF ECPR INITIATION FOR REFRACTORY OHCA**

Three approaches are currently used for ECPR initiation in patients with refractory OHCA: initiation at an ECPR-capable hospital,prehospital initiation, and the rendezvous approach. The most commonly used approach is intra-arrest transport to an ECPR-capable hospital followed by initiation of ECPR at the hospital. The three published randomized trials on ECPR [20–22] followed this approach. Initiation of ECPR with this approach is the least complicated, because ECPR is typically performed by experienced providers at a high-volume ECMO center. However, with this approach, only a limited number of patients can receive ECPR within acceptable timeframes, because on-scene resuscitation and transport to a hospital usually take a significant amount of time. ECPR is only performed at a small number of tertiary hospitals, limiting the geographic coverage of ECPR. To overcome this limitation, alternative approaches including the prehospital initiation and rendezvous approach have been developed. In the rendezvous approach, an ECPR candidate is transferred to a hospital closer to the scene of arrest while an ECMO cannulation team is deployed to that hospital. The patient undergoes ECPR in the rendezvous hospital and is transferred to an ECMO center for postresuscitation care. The investigators of the ARREST trial extended their ECMO-facilitated resuscitation program to the Minneapolis–St. Paul metropolitan area using this approach and reported achieving a neurologically favorable survival rate similar to that in the ARREST trial (43%) [120]. Several systems, including the Service d’Aide Médicale Urgente of Paris, have adopted prehospital ECPR, which brings ECMO to patients with OHCA instead of taking the patients to an ECMO-capable center [26,121,122]. Lamhaut et al. [26] compared the mean CPR duration and survival rate before and after a change in the ECPR strategy in 156 patients treated with ECPR and reported a shorter mean CPR duration and higher...
survival rate in the prehospital ECPR-based strategy than in the strategy that allowed liberal allocation between prehospital or in-hospital ECPR.

Several studies have suggested that the prehospital ECPR or rendezvous approach could allow more patients to receive ECPR than initiation on arrival to an ECPR-capable hospital [123,124]. Song et al. [124] quantified patient catchment areas of the three approaches in Sydney, Australia, and reported that the rendezvous (n = 2,175,096) and prehospital ECPR models (n = 3,851,727) substantially increased the catchment of eligible patients with OHCA compared to the in-hospital ECPR model (n = 811,091). However, implementation of ECPR using these approaches is challenging. Both the rendezvous and prehospital ECPR approaches require substantial planning, training, and logistics efforts and highly coordinated collaboration between prehospital EMS and ECMO centers. The optimal approach for ECPR remains elusive, but may vary depending on geographical characteristics, population density, and medical resources of the region. The ECPR-capable hospital-based approach may be effective if multiple ECPR-capable hospitals are sufficiently dispersed across the region to handle most patients requiring ECPR. However, this is not the case in most regions, wherein the rendezvous approach or prehospital ECPR may be desirable to maximize the coverage of ECPR service.

CONSIDERATIONS FOR INCORPORATING ECPR WITHIN A SYSTEM OF CARE

All elements of the system of care for resuscitation of patients with cardiac arrest should be optimized to achieve neurologically favorable survival with ECPR. Efforts to increase provision of bystander CPR may improve outcomes of patients undergoing ECPR and increase the number of patients receiving ECPR [31]. Most patients with refractory OHCA are not eligible for ECPR due to a prolonged CPR time [125]. Efforts to reduce the time from cardiac arrest to ECMO initiation may therefore be critically important for successful ECPR implementation. Read et al. [126] reported a significant reduction in the time from cardiac arrest to ECMO initiation after implementing a dedicated simulation program for ECPR. Early communication and effective coordination between EMS and ECMO centers are also critical in limiting the time from cardiac arrest to ECMO initiation.

ECPR is only one part of the system of care for resuscitation of patients with cardiac arrest. Only a minority of patients with OHCA are ultimately considered suitable for ECPR [26,127,128]. Changes in EMS for successful ECPR implementation should not hinder resuscitation of patients not receiving ECPR. Intra-arrest transport for in-hospital ECPR can compromise CPR quality during transport, thus adversely affecting outcomes of patients not receiving ECPR [129,130]. Therefore, in cases of hospital-based ECPR, efforts should be made to select ECPR candidates requiring intra-arrest transport and to maintain high-quality CPR during intra-arrest transport (e.g., mechanical CPR).

ECPR requires a high level of expertise and experience. A recent study reported a significant association between higher ECPR case volume and improved survival [73]. ECPR-specific simulation training may help clinicians to develop and maintain the skills and experience needed to expeditiously and safely perform ECPR. Several studies have reported significantly reduced the time to ECMO initiation after ECPR-specific simulation training [126,131].

CONCLUSION

The efficacy of ECPR over conventional treatment in patients with refractory OHCA remains unclear. ECPR may render significant survival benefits over conventional CPR in selected patients only when performed with strict protocol adherence in an experienced system and with a high level of collaboration between EMS and ECMO centers. ECPR is only one part of the system of care for resuscitation of cardiac arrest victims. Optimizing the chain of survival is critical to improving outcomes of patients receiving ECPR.

ETHICS STATEMENT

Not applicable.

CONFLICT OF INTEREST

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

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AUTHOR CONTRIBUTIONS

Conceptualization: all authors; Visualization: YHJ; Writing—original draft: KWJ, YHJ; Writing—review & editing: all authors. All authors read and approved the final manuscript.

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Optimal extracorporeal CPR use strategy


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Reduced-dose systemic fibrinolysis in massive pulmonary embolism: a pilot study

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Objective Severe pulmonary embolism (PE) has a high mortality rate, which can be lowered by thrombolytic therapy (TT). However, full-dose TT is associated with major complications, including life-threatening bleeding. The aim of this study was to explore the efficacy and safety of extended, low-dose administration of tissue plasminogen activator (tPA) on in-hospital mortality and outcomes in massive PE.

Methods This was a single-center, prospective cohort trial at a tertiary university hospital. A total of 37 consecutive patients with massive PE were included. A peripheral intravenous infusion was used to administer 25 mg of tPA over 6 hours. The primary endpoints were in-hospital mortality, major complications, pulmonary hypertension, and right ventricular dysfunction. The secondary endpoints were 6-month mortality and pulmonary hypertension and right ventricular dysfunction 6 months after the PE.

Results The mean age of the patients was 68.76±14.54 years. The mean pulmonary artery systolic pressure (PASP; 56.51±7.34 mmHg vs. 34.16±2.81 mmHg, P < 0.001) and right/left ventricle diameter (1.37±0.12 vs. 0.99±0.12, P < 0.001) decreased significantly after TT. Tricuspid annular plane systolic excursion (1.43±0.33 cm vs. 2.07±0.27 cm, P < 0.001), myocardial performance index (0.47±0.08 vs. 0.55±0.07, P < 0.001), and systolic wave prime (9.6±2.8 vs. 15.3±2.6) increased significantly after TT. No major bleeding or stroke was observed. There was one in-hospital death and two additional deaths within 6 months. No cases of pulmonary hypertension were identified during follow-up.

Conclusion The results of this pilot study suggest that an extended infusion of low-dose tPA is a safe and effective therapy in patients with massive PE. This protocol was also effective in decreasing PASP and restoring right ventricular function.

Trial registration: ClinicalTrials.gov identifier: NCT02029456

Keywords Pulmonary embolism; Thrombolytic therapy; Echocardiography; Low-dose tissue plasminogen activator

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INTRODUCTION

Pulmonary embolism (PE) is a life-threatening disease requiring early diagnosis and treatment. Thrombolytic therapy (TT) is often required in patients with massive PE [1]. Severe PE has a high mortality rate, and the in-hospital all-cause case mortality rates among unstable patients who receive TT are lower than among those who do not [1]. However, only a minority (≤ 30%) of unstable patients actually receive TT [2,3] for reasons that remain unclear. The high rate of complications associated with TT, including life-threatening bleeding, and insufficient data from the massive PE population might explain the reluctance to use TT.

The lungs are the only organ to receive the entire cardiac output, which makes them the point of convergence for all of an administered thrombolytic agent, independent of the route of administration. Therefore, lowering the dose of TT might both maintain its effectiveness in patients with massive PE and enhance its safety profile. Percutaneous endovascular interventions for deep venous thrombosis have suggested that low-dose thrombolysis can induce a favorable pulmonary response [4]. The aim of the present pilot study was to explore the efficacy and safety of an extended administration (6 hours) of low-dose (25 mg) tissue plasminogen activator (tPA) in patients with massive PE.

METHODS

Ethics statement
This study was approved by the Institutional Review Board of the University of Health Sciences Ahi Evren Chest Cardiovascular Surgery Education and Research Hospital (No. 2014-02029456), and patients were enrolled after providing informed consent. This study conforms with the principles of the Helsinki declaration and is registered in ClinicalTrials.gov (identifier: NCT02029456).

Patient population and enrollment
This single-center, prospective observational pilot study explored the effectiveness of an extended administration of low-dose TT in treating massive PE. We hypothesized that the most serious complication of TT (bleeding) could be diagnosed early, and that a slow, low-dose TT infusion could be stopped immediately. We did not use concomitant heparin anticoagulation with TT due to the potential increased risk of bleeding.

Between May 2011 and May 2014, we enrolled 37 consecutive patients aged 18 years or older with confirmed massive PE (Fig. 1). PE was defined according to current guidelines as patients presenting with signs and symptoms suggestive of PE plus imaging documentation of PE on computed-tomographic angiography [1]. Massive PE was defined as acute PE with sustained hypotension (systolic blood pressure < 90 mmHg for at least 15 minutes or a need for inotropic support that was not due to a cause other than PE, such as arrhythmia, hypovolemia, sepsis, or left ventricular [LV] dysfunction), pulselessness, or persistent profound bradycardia (heart rate < 40 beats/min with signs or symptoms of shock). Patients with a prior intracranial hemorrhage, known structural intracranial cerebrovascular disease (e.g., arteriovenous malformation), known malignant intracranial neoplasm, ischemic stroke within 3 months, suspected aortic dissection, active bleeding or bleeding diathesis, recent surgery encroaching on the spinal canal or brain, or recent significant closed-head or facial trauma with radiographic evidence of bony fracture or brain injury were excluded from the study. The patient demographic characteristics, medical history, rhythm disorders, New York Heart Association (NYHA) classification, and primary symptoms were prospectively entered into a database.

Echocardiography
Each patient underwent a transthoracic echocardiographic evaluation before the TT, within an hour after the TT, before discharge (5–7 days), and a month after the TT. Pulmonary artery systolic
Reduced-dose systemic fibrinolysis in massive PE

Pressure (PASP) was estimated from the tricuspid valve regurgitant jet velocity using the modified Bernoulli equation: $4v^2 + \text{right atrial pressure}$ [5]. The maximum dimensions of the right/left atria were measured in the standard four-chamber view. The diameter and collapsibility of the Inferior vena cava were noted. Pulmonary hypertension was defined as a PASP of > 40 mmHg. Right ventricular (RV) enlargement was defined as an RV/LV ratio of > 0.9. Tricuspid annular plane systolic excursion (TAPSE), tissue-Doppler–derived tricuspid annular systolic velocity, and the myocardial performance index (MPI), or Tei index, were recorded.

Computed tomography
All patients underwent 64-slice computed-tomographic pulmonary angiography (Aquilion 64, Toshiba Medical Systems) upon admission to the hospital to definitively diagnose PE. Patients underwent additional computed-tomographic angiography 24 hours after the completion of TT if their estimated glomerular filtration rate was > 60 mL/min/1.73 m² according to the modified diet in renal disease formula.

Thrombolytic therapy
After the diagnosis of massive PE, a 6-hour intravenous infusion of 25 mg of tPA without a bolus was administered. Anticoagulation with intravenous unfractionated heparin was withheld during thrombolytic agent infusion. Heparin, administered as a 70-U/kg bolus followed by a 1,000-U/hr infusion with a target activated partial thromboplastin time between 1.5 and 2.5 times the control was started immediately after the infusion of thrombolytic agent. After successful thrombolysis, warfarin was restarted while the patient was still on intravenous heparin.

Criteria for thrombolytic success
The following are the criteria for thrombolytic success: (1) Doppler documentation of the resolution of high PASP (< 40 mmHg); (2) decreased right ventricular diameter (at least 25% decrease of RV/LV diameter); (3) restoration of RV function (TAPSE > 16 mm); (4) systolic wave prime (S') > 10.0 cm/sec; (5) tissue-Doppler–derived RV MPI > 0.55; and (6) clinical improvement of symptoms and restoration of stable hemodynamic status immediately after TT. Complete success was defined as clinical improvement of symptoms and restoration of stable hemodynamic status with at least three of the other criteria and without resultant death or nonfatal major complications.

The primary endpoints in this study were in-hospital mortality, nonfatal major complications, the development of pulmonary hypertension, and RV dysfunction. The secondary endpoints were 6-month mortality and pulmonary hypertension and RV dysfunction at 6 months.

Definition of complications
The definitions of complications used are the following: (1) in-hospital mortality; (2) nonfatal major complications (ischemic stroke, intracranial hemorrhage, embolism [coronary or peripheral], bleeding requiring transfusion); and (3) nonfatal minor complications (bleeding not requiring transfusion [bleeding resulting in a hemoglobin drop < 3 g/dL]).

Statistical analysis
Analyses were conducted using SPSS ver. 17.0 (SPSS Inc). Continuous variables are expressed as the mean ± standard deviation for parameters with a normal distribution or median (interquartile range) for parameters with a non-normal distribution. Categorical variables are expressed as percentages. The analysis of normality was performed with the Kolmogorov-Smirnov test. Repeated-measure analysis of variance testing was used to analyze the dependent variables. The Bonferroni test was used as a post hoc analysis to adjust for multiple comparisons. A two-sided $P < 0.05$ was considered significant.
RESULTS

This trial enrolled 37 consecutive patients (15 male patients) with massive PE. The mean age of the patients was 68.76 ± 14.54 years, and 22 patients (59.5%) were older than 70 years. The baseline clinical characteristics of the patients are presented in Table 1. Twenty-two patients (59.5%) had hypertension, seven patients (18.9%) had diabetes mellitus, 12 patients (32.4%) had chronic obstructive pulmonary disease, eight patients (21.6%) had coronary artery disease, and five patients (13.5%) had congestive heart failure. Seventeen patients (45.9%) had accompanying deep venous thrombosis. All patients were followed for 6 months. The most common symptoms on admission were dyspnea and palpitations (Table 1). All the patients were hypotensive, and their mean systolic and diastolic blood pressures at admission were 76.19 ± 8.52 and 49.62 ± 7.82 mmHg, respectively. Blood pressure recovered within a few hours after the initiation of TT in all cases. The median troponin values (0.4 ng/mL; interquartile range, 0.30–0.76 ng/mL) were elevated at hospital admission. The mean length of hospital stay was 6.1 ± 1.07 days (Table 2). Of the 37 patients, 18 (48.6%) underwent repeat pulmonary computed tomography 24 hours after TT. Of those 18 patients, total lysis of the thrombus was observed in 16 patients (88.9%), and the remaining two patients had >75% lysis of the thrombus.

Echocardiography results

The echocardiographic variables are reported in Table 3. The mean PASP decreased significantly after TT (56.51 ± 7.34 mmHg vs. 34.16 ± 2.81 mmHg, P < 0.001) and continued to decrease significantly until discharge (34.16 ± 2.81 mmHg vs. 30.35 ± 3.19 mmHg, P < 0.001). The mean PASP was preserved at the 6-month follow-up visit (28.70 ± 3.04 mmHg), and none of the patients had pulmonary hypertension. The mean TAPSE increased significantly after TT (1.43 ± 0.33 cm vs. 2.07 ± 0.27 cm, P < 0.001). The MPI index steadily and significantly improved after TT (0.47 ± 0.08 vs. 0.55 ± 0.07, P < 0.001). The S′ increased significantly after TT (9.6 ± 2.8 cm/sec vs. 15.3 ± 2.6 cm/sec), and the RV/LV diameter steadily and significantly decreased after TT (1.37 ± 0.12 vs. 0.99 ± 0.12, P < 0.001).

Table 1. Baseline patient characteristics (n=37)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>68.76±14.54</td>
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<tr>
<td>≥ 70</td>
<td>22 (59.5)</td>
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<tr>
<td>Male sex</td>
<td>15 (40.5)</td>
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<tr>
<td>Hypertension</td>
<td>22 (59.5)</td>
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<tr>
<td>Diabetes mellitus</td>
<td>7 (18.9)</td>
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<td>Chronic obstructive pulmonary</td>
<td>12 (32.4)</td>
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<tr>
<td>disease</td>
<td>8 (21.6)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>10 (27.0)</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>5 (13.5)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>6 (16.2)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>6 (16.2)</td>
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<tr>
<td>Cancer</td>
<td>7 (18.9)</td>
</tr>
<tr>
<td>Previous venous thromboembolism</td>
<td>2 (5.4)</td>
</tr>
<tr>
<td>Oral contraceptive</td>
<td>8 (21.6)</td>
</tr>
<tr>
<td>Obesity</td>
<td>10 (27.0)</td>
</tr>
<tr>
<td>Immobilization</td>
<td>6 (16.2)</td>
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<tr>
<td>Recent major surgery</td>
<td>17 (45.9)</td>
</tr>
<tr>
<td>Concomitant deep venous</td>
<td>18 (48.6)</td>
</tr>
<tr>
<td>thrombosis</td>
<td>37 (100)</td>
</tr>
<tr>
<td>Syncope</td>
<td>37 (100)</td>
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<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>76.19±8.52</td>
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<td>Heart rate (beats/min)</td>
<td>121.10±10.65</td>
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<td>Respiratory rate (breaths/min)</td>
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<td>Peripheral oxygen saturation (%)</td>
<td>84.68±8.64</td>
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<tr>
<td>Troponin-I (ng/mL)</td>
<td>0.4 (0.30–0.76)</td>
</tr>
</tbody>
</table>

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

*Obesity was defined as body mass index ≥ 30 kg/m².

Table 2. Primary and secondary outcomes (n=37)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital stay (day)</td>
<td>6.1 ± 1.07</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>1 (2.7)</td>
</tr>
<tr>
<td>6-mo Mortality</td>
<td>3 (8.1)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

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

Table 3. Echocardiographic outcomes of patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>On admission</th>
<th>Post-TT</th>
<th>Predischarge</th>
<th>6-mo Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASP (mmHg)*</td>
<td>56.51 ± 7.34</td>
<td>34.16 ± 2.81</td>
<td>30.35 ± 3.19</td>
<td>28.70 ± 3.04</td>
</tr>
<tr>
<td>TAPSE (cm)*</td>
<td>1.43 ± 0.33</td>
<td>2.07 ± 0.27</td>
<td>2.17 ± 0.22</td>
<td>2.21 ± 0.22</td>
</tr>
<tr>
<td>MPI*</td>
<td>0.47 ± 0.08</td>
<td>0.55 ± 0.07</td>
<td>0.59 ± 0.04</td>
<td>0.61 ± 0.03</td>
</tr>
<tr>
<td>S′ (cm/sec)*</td>
<td>9.60 ± 2.80</td>
<td>15.30 ± 2.60</td>
<td>16.10 ± 2.20</td>
<td>16.90 ± 2.40</td>
</tr>
<tr>
<td>RV/LV diameter*</td>
<td>1.37 ± 0.12</td>
<td>0.99 ± 0.12</td>
<td>0.84 ± 0.10</td>
<td>0.67 ± 0.10</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.

*On admission vs. post-TT, P < 0.001; on admission vs. predischarge, P < 0.001; on admission vs. 6-month follow-up, P < 0.001. Post-TT vs. predischarge: PASP, P < 0.001; TAPSE, P = 0.042; MPI, P = 0.001; S′, P = 0.197; RV/LV diameter, P < 0.001. Post-TT vs. 6-month follow-up: PASP, P < 0.001; TAPSE, P = 0.001; MPI, P < 0.001; S′, P = 0.011; RV/LV diameter, P < 0.001. Predischarge vs. 6-month follow-up: PASP, P = 0.016; TAPSE, P = 0.255; MPI, P < 0.001; S′, P = 0.178; RV/LV diameter, P < 0.001.

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TREATMENT

No major bleeding events were observed. Three patients had minor bleeding: two patients had epistaxis, and the remaining patient had gingival bleeding. The two episodes of epistaxis were observed 2 days after TT, and the gingival bleeding was observed 3 days after TT. All the bleeding events occurred during heparin infusion, stopped with gentle compression, and did not recur. None of the patients had a stroke or transient ischemic attack during hospitalization. One patient (3.1%) died in the hospital on the 6th day of hospitalization due to a malignant ventricular arrhythmia. That patient had ischemic dilated cardiomyopathy (LV ejection fraction of 20%) and acute on chronic renal failure.

CLINICAL COURSE

Overall, one patient died in the hospital, and two patients died during follow-up, both with malignancy. Pulmonary hypertension did not develop during follow-up. None of the patients had recurrent deep venous thrombosis, PE, or RV dysfunction during the follow-up period. All patients had a favorable functional class at their follow-up visit. During follow-up after discharge, six of the 34 patients (17.6%) had major bleeding, and two patients (5.8%) had minor bleeding (according to the Thrombolysis in Myocardial Infarction [TIMI] bleeding criteria) due to warfarin.

DISCUSSION

The present pilot study suggests that an extended infusion of low-dose tPA is safe and effective in treating massive PE. TT was associated with a significant early reduction in PASP and improved RV function that were maintained through the 6-month follow-up. Low-dose thrombolysis with extended administration appears to be a promising option in advanced therapy for massive PE and warrants further study in a larger, randomized controlled trial.

Massive PE is a deadly disease with a reported mortality rate of up to 52.4%, which increases to 65% in patients requiring cardiopulmonary resuscitation [3,6]. Although TT can be lifesaving, studies have indicated that only 30% of massive PE patients receive TT [2,3].

Massive PE patients who were elderly or had comorbidities were less likely than others to receive TT, but those who received TT had a lower in-hospital fatality rate irrespective of their age or comorbid conditions [7]. TT-associated complications, especially major bleeding, might be an important factor in this reluctance to treat, and the risk of TT-associated major bleeding does increase with age [8]. Fiumara et al. [9] revealed that major bleeding was more frequent in unstable patients with PE than in stable patients. The most fearful complication of TT is intracerebral hemorrhage. Constantinides et al. [10] reported that TT was associated with a major bleeding rate of 21.9% in patients with massive PE. Levine [11] reported an 8.4% incidence of major bleeding and a fatal hemorrhage rate of 2.2% in patients receiving TT for PE. The International Cooperative Pulmonary Embolism Registry reported a 3% incidence of intracerebral hemorrhage [3].

Lowering the TT dose might decrease complications. In the MOPETT (Moderate Pulmonary Embolism Treated with Thrombolysis) trial, Sharifi et al. [12] reported that a lower dose of tPA (50 mg) was safe and effective in treating moderate PE without any cases of major bleeding. That study was performed in patients with moderate PE, and TT was administered as a 10 mg tPA bolus followed by a 40 mg infusion over 2 hours. Recently, Ozkan et al. [13] reported that an extended low-dose infusion of tPA (25 mg tPA in 6 hours) was safe and effective in patients with a prosthetic valve thrombosis. Furthermore, that regimen was also safe and effective for pregnant patients with prosthetic valve thrombosis [14]. In their series, no patient who received an extended infusion of low-dose TT had major bleeding. A few case reports in the literature report on the safety and effectiveness of a prolonged infusion of low-dose TT in very elderly patients with massive PE, who have a high bleeding risk and other contraindications to TT [15–18]. No patients in our study had fatal or even major bleeding. Overall, three patients in this study had minimal bleeding 48–72 hours after completing TT and during heparin therapy (likely unrelated to the administration of TT).

TT augments the restoration of lung perfusion, whereas patients treated with heparin have no substantial improvement in pulmonary blood flow [19–23]. The MOPETT trial showed that lower dose tPA (50 mg) decreased PASP more effectively than heparin therapy alone, and that difference remained apparent during long-term follow-up [12]. We found that an extended infusion of an even lower dose (25 mg) of tPA was still effective in both decreasing PASP and restoring RV function. PASP, TAPSE, the RV MPI, and tissue-Doppler–derived tricuspid lateral annulus systolic motion all improved after TT, and those effects were maintained at the 6-month mark. None of the patients developed pulmonary hypertension during follow-up. Furthermore, no recurrent PE occurred in this study population during follow-up.

There were several limitations in our study. Our study is a single-center, nonrandomized, observational study. The absence of a comparison group receiving standard therapy is a major weakness of this observational trial. This study is not a head-to-head comparison between an extended infusion of low-dose tPA and the standard dose regimen for treating massive PE. However, it is a sizable pilot cohort for this specific study population. All patients with
massive PE were treated similarly in our hospital. Furthermore, our relatively small sample size might be underpowered to detect relatively infrequent risks.

In conclusion, our pilot study suggests that an extended infusion of low-dose tPA is a safe and effective therapy in patients with massive PE. This protocol was also effective in decreasing PASP and restoring RV function.

ETHICS STATEMENT

This study was approved by the Institutional Review Board of the University of Health Sciences Ahi Evren Chest Cardiovascular Surgery Education and Research Hospital (No. 2014-02029456), and patients were enrolled after providing informed consent. This study conforms with the principles of the Helsinki declaration and is registered in ClinicalTrials.gov (identifier: NCT02029456).

CONFLICT OF INTEREST

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

FUNDING

None.

AUTHOR CONTRIBUTIONS

Conceptualization: ACA; Data curation: ACA, IG, CYK; Formal analysis: ACA, IG, CYK, SDW; Investigation: ACA, TG, IG, EK, FB, EH; Methodology: ACA; Supervision: ACA; Writing—original draft: ACA, CYK, SDW; Writing—review & editing: all authors. All authors read and approved the final manuscript.

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REFERENCES

Reduced-dose systemic fibrinolysis in massive PE

Influence of work and family environment on burnout among emergency medical technicians

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Objective Burnout among emergency medical technicians is a serious problem affecting delivery of quality emergency medical services. Although the repetitive nature of the job and lower education level requirements for technicians have been reported as risk factors, little is known about the influence of burden of responsibility, degree of supervisor support, and home environment on burnout among emergency medical technicians. This study aimed to test the hypothesis that burden of responsibility, degree of supervisor support, and home environment increase burnout probability.

Methods A web-based survey was conducted among emergency medical technicians in Hokkaido, Japan from July 26, 2021 to September 13, 2021. A total of 21 facilities were randomly selected from 42 fire stations. Prevalence of burnout was measured using the Maslach Burnout-Human Services Survey Inventory (MBI-HSS). Burden of responsibility was measured using a visual analog scale. Occupational background was also measured. Supervisor support was measured using the Brief Job Stress Questionnaire (BJSQ). Family-work negative spillover was measured using the Japanese version of Survey Work–Home Interaction–NijmeGen (SWING). The cutoff value for burnout syndrome was defined as emotional exhaustion ≥ 27 and/or depersonalization ≥ 10.

Results A total of 700 survey respondents were included, and 27 surveys with missing data were excluded. The suspected burnout frequency was 25.6%. Covariates were adjusted using multilevel logistic regression model analysis. Low supervisor support (odds ratio, 1.421; 95% confidence interval, 1.136–1.406; P < 0.001) and high family-work negative spillover (odds ratio, 1.264; 95% confidence interval, 1.285–1.571; P < 0.001) were independent factors associated with higher probability of burnout.

Conclusion This study indicated that focusing on improvement of supervisor support for emergency medical technicians and creating supportive home environments may assist in reducing burnout frequency.

Keywords Psychological burnout; Emergency medical technicians; Home environment
INTRODUCTION

Emergency medical services (EMS) play a critical role in providing care to patients in prehospital settings worldwide. The EMS field evolved in the 1960s due to the occurrence of traffic traumas and has been expanding in influence [1]. The educational system for emergency medical technicians (EMTs) and practice environment in which EMTs work vary from country to country. In the United States, there are four levels of EMS professionals certified by the National Registry of Emergency Medical Technicians: emergency medical responder, EMT, advanced EMT, and paramedic [2]. In addition, the legal authority and regulatory responsibilities of EMTs is at a state level, not federal. Thus, the structure, delivery, and funding of EMS vary from state to state, as does the scope of work. Therefore, the educational requirements of each EMS provider also vary. EMS has a wide variety of forms, including attachment to fire department systems, medical center systems, nonprofit organizations, private companies, and government agencies [3].

There are two levels of EMT professionals in Japan: EMTs and paramedics [4]. EMTs are affiliated with each municipality and responsible for driving ambulances, providing first aid to patients in these ambulances, and transporting patients to emergency facilities. Japan’s emergency medical care system is classified into the following: primary emergency facilities, mainly providing outpatient services; secondary emergency facilities, predominantly treating severely ill patients who require hospitalization; and emergency medical centers, treating severely ill patients who require advanced treatment [4]. Patients who cannot visit the hospital independently are transported to an emergency hospital by ambulances, which is requested by either patients or their family members. In 2017, there were 6,342,147 ambulance dispatches in Japan, a consistent increase since 2004 [5]. Currently, the scope of prehospital emergency care in any country is no longer limited to traffic traumas [4]. The role of EMTs has also diversified due to changes in the nature of diseases, such as cardiac disease and acute exacerbations of chronic diseases, and populations [6]. Therefore, medical care in prehospital settings is a common entry point into the continuum of care. In addition, presence of EMTs is essential to providing the necessary medical care in the prehospital setting.

However, fatigue and stress among healthcare professionals involved in EMS have become problematic. In particular, burnout is one of the most widely discussed mental health problems in society. The concept of burnout was first described by Freudenberger [7]. He described burnout in the workplace as “exhaustion due to excessive demands on energy, stamina, and resources.” The processual characteristics of burnout indicate the cumulative negative consequences of long-term work stress and fatigue [8]. Burnout has been reported to produce physical symptoms such as fatigue, malaise, frequent headaches and gastrointestinal problems, insomnia, and shortness of breath, as well as psychological conditions such as frustration, anger, and depression [9]. Burnout in healthcare professionals has been associated with depression, suicidal ideation, early retirement, and medication errors [10,11]. Risk factors for burnout among healthcare professionals involved in emergency medicine have been reported to include age, gender, education, years of experience, degree of supervisor support, family-to-work negative spillover (FWNS), and caring for critically ill patients [15,16].

EMTs are involved in providing first aid to patients with sudden illnesses, and EMTs are responsible for transporting patients quickly to the hospital. The occupational environment in which EMTs work is characterized by regular exposure to traumatic and emotionally taxing situations [2], a dynamic and uncontrolled environment with frequent changes, increased rates of occupational violence [17], physical fatigue [18], irregular work patterns [19], long overtime hours [20], and higher workload [21]. Burnout has been reported to range between 16% and 56% [22] among EMTs, indicating a burnout rate similar to that among emergency physicians and intensivists [14]. The risk factors for burnout among
EMTs have been reported to include years of doing the same job, work location [23], and work overload [24]. FWNS is reflected through several risk factors that include impact of a poor family environment on work [25], work environment [26], and degree of supervisor support [27]. These are independent risk factors for burnout. Moreover, EMTs tended to experience increased stress and responsibility due to encountering stressful situations, such as providing care for patients with trauma or cardiopulmonary arrest [28]. Rescuing a patient with a life-threatening condition can present a huge burden of responsibility. Situations involving serious responsibilities in prehospital medicine may be associated with burnout in EMTs. However, this has not yet been researched. Therefore, we hypothesized that burnout among EMTs would be associated with FWNS, low supervisor support, and a high burden of responsibility.

**METHODS**

**Ethics statement**

This study was approved by a suitably constituted Ethics Committee of Sapporo Medical University (No. 2-1-76) and conformed to the provisions of the Declaration of Helsinki. Informed consent was obtained from all the respondents prior to the survey.

**Study design and settings**

An institution-based, cross-sectional study was conducted among 3,215 EMTs in Hokkaido, Japan using ArcGIS Survey 123 (Esri, https://survey123.arcgis.com/) from July 26, 2021 to September 13, 2021. ArcGIS Survey 123 is a platform that maintains a high level of security.

Simple random sampling was used to select 42 fire stations in Hokkaido, Japan after obtaining permission from the chief of each fire station. The number of EMTs in each fire department was identified. We emailed heads of selected fire stations requesting a response from the EMTs.

Hokkaido's EMS system is operated by local fire departments and can be activated by a 119 call from anywhere in Hokkaido [29]. In 2021, a total of 42 fire departments and 427 ambulances were deployed in Hokkaido [30]. Usually, each ambulance has a crew of three emergency providers, including at least one emergency life-saving technician and a highly trained prehospital emergency care provider. On-site EMS personnel select hospitals for patient transport, including tertiary care hospitals, with the capacity to manage patients with life-threatening conditions. Local medical management councils, composed of emergency physicians and specialists from each region of Japan, play an important role in ensuring the quality of care provided by EMS staff in prehospital settings and in conducting follow-up evaluations of EMS procedures [31].

**Measurement**

The survey comprised six components. The first part of the questionnaire, on individual and organizational characteristics, included age, gender, marital status, bachelor's degree as education status, managerial position, full-time employment status, paramedic certification, population of the employment area, years of doing the same job, and type of fire department. The second part concerned the working environment, such as the number of annual mobilizations, night shifts, hours worked per week, overtime hours, and number of paid vacations taken per year. Another included variable was the frequency of involvement of the EMT personnel in the transport of COVID-19 patients, as the COVID-19 pandemic may increase burnout among EMTs. The third component consisted of the 22-item Maslach Burnout-Human Services Survey (MBI-HSS) [32], which was used to assess burnout among EMTs. The fourth component consisted of a nine-item subscale of the Brief Job Stress Questionnaire (BJSQ) to assess the level of support from superiors [33]. The BJSQ has been authorized by the Ministry of Health, Labour and Welfare of Japan and is considered a standard questionnaire for evaluating occupational stress [34]. The fifth component consisted of four items from the Japanese version of Survey Work–Home Interaction – NijmeGen (SWING-J) to assess the FWNS of EMTs [35]. The sixth component consisted of three questions to assess the burden of responsibility of the paramedic's work.

The MBI-HSS is widely used to assess burnout and consists of three dimensions: emotional exhaustion (EE), depersonalization (DP), and personal accomplishment. This Japanese-translated instrument has been validated [36]. The alpha for each factor in the reliability of the Japanese version of the MBI-HSS was 0.92, 0.91, and 0.88, respectively. Each question was rated on a 7-point Likert scale (0 [never] to 6 [frequent]). The cutoff value for burnout syndrome was defined as EE ≥ 27 and/or DP ≥ 10. The cutoff scores used in this study were based on a 2016 systematic review, which is identified as the most widely used criteria to define burnout [37].

The BJSQ was developed to measure occupational stress but could also gauge the degree of supervisor support [33]. For each of the BJSQ subscales, respondents rated their level of agreement on a standard 4-point Likert scale (1 [strongly disagree] to 4 [strongly agree]). A higher score on the subscale of supervisor support indicates a greater need for supervisor support for EMTs.

SWING-J was developed as a scale to assess work–home interactions. Geurts et al. [38] defined FWNS as negative load reactions transferred from domestic space to the workplace. For each
First, to determine the contents of the questions regarding the burden of responsibility on EMTs, first, the available information from previous studies was examined [24,39,40]. Second, parametric perceptions concerning their burden of responsibility in their work were extracted. Third, based on these contents, 10 EMTs were interviewed to analyze the tasks for which the EMTs assumed responsibility. Based on these results, three items were adopted in this study: (1) burden of responsibility in determining the medical condition of the patient; (2) burden of responsibility in selecting a hospital to transport the patient; and (3) burden of responsibility in communicating with physicians. Each question was measured using the visual analog scale (VAS) with "strongly agree" as 100 and "disagree" as 0.

Bias
Simple random sampling was used to select the participants of the study from the fire station of each region. This was done to address the potential selection and response biases. Therefore, selection bias did not have a significant impact on the results of this study. In addition, there were some confounding factors, such as years of doing the same job, marital status, shift, and position, which could have influenced burnout [22]. Therefore, multivariate statistics were used to make adjustments for these factors.

Sample size
The prevalence of burnout was estimated at 20% [22], and 12 covariates were identified that required adjustment in logistic regression. As a result, the number of participants needed for the analysis was estimated to be 650 [41], and considering a response rate of 20%, a sample size of 3,250 was considered necessary.

Statistics
Normally distributed data are represented as mean ± standard deviation. Non-normally distributed data are presented as median (interquartile range [IQR]). First, descriptive statistics were calculated. Second, the respondents’ demographic characteristics, burden of responsibility, working environment, social support, and work-life balance were compared with those of EMTs with or without burnout using Fisher exact test for categorical variables or the t-test for continuous variables. Third, to clarify the relationship between burnout and FWNS, supervisor support, and severity of responsibility, a multilevel logistic regression analysis was performed using SWING-J and BJSQ scores as continuous variables. The VAS scores of the three items of severity of responsibility that were significantly different in the univariate analysis were continuous variables in this logistic regression analysis. Therefore, covariates were introduced at the fire department level to account for the possible heterogeneity in fire department management practices. Items from the three burdens of responsibility that showed significant differences using the univariate analysis were analyzed using multilevel logistic regression analysis. The covariates were predefined based on previous studies and clinical perspectives. The covariates were predefined based on previous studies and clinical perspectives [23,39]. The covariates were years of doing the same job, education, experience in transporting patients with COVID-19, marital status, full-time employment of EMTs and paramedics, shift, and position.

The results of multilevel logistic regression model analysis are shown with odds ratios (ORs), 95% confidence intervals (CIs), and P-values. A P-value of < 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS ver. 27 (IBM Corp).

RESULTS

Population
A total of 700 respondent surveys were included in the final analysis after excluding 27 surveys with missing data. The response rate was 21.8%. The survey respondents’ characteristics are presented in Table 1. A total of 86.3% of respondents were involved in COVID-19 patient management.

Associations of work and personal environments and the outcomes of burnout
Table 1 shows the comparison of the characteristics, supervisor support, and FWNS between respondents with and without burnout. In the univariable analysis, EMTs with bachelor’s degrees had a significantly higher probability of burnout than EMTs without bachelor’s degrees (12.8% vs. 7.5%, P = 0.033). Full-time EMTs had a significantly higher probability of burnout than other EMTs (P < 0.001). The VAS score for the burden of responsibility in communicating with physicians was significantly higher in respondents than in those without (76.7 ± 26.7 vs. 70.9 ± 26.6, P = 0.013). Supervisor support scores were significantly higher in respondents with burnout than in those without (8.1 ± 2.1 vs. 6.6 ± 2.1, P < 0.001). The FWNS scores were significantly higher in respondents with burnout than in those without (1.9 ± 2.1 vs. 1.0 ± 1.4, P < 0.001).
Table 1. Characteristics of the respondents and associations of work, personal environments, supervisor support scores, and FWNS with burnout

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall (n = 700)</th>
<th>Burnout (Yes n = 179)</th>
<th>Burnout (No n = 521)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>685 (97.9)</td>
<td>174 (97.2)</td>
<td>511 (98.1)</td>
<td>0.550</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
<td>0.202</td>
</tr>
<tr>
<td>20–29</td>
<td>213 (30.4)</td>
<td>48 (26.8)</td>
<td>165 (31.7)</td>
<td></td>
</tr>
<tr>
<td>30–39</td>
<td>230 (32.9)</td>
<td>54 (30.2)</td>
<td>176 (33.8)</td>
<td></td>
</tr>
<tr>
<td>40–49</td>
<td>207 (29.6)</td>
<td>60 (33.5)</td>
<td>147 (28.2)</td>
<td></td>
</tr>
<tr>
<td>50–59</td>
<td>48 (6.9)</td>
<td>17 (9.5)</td>
<td>31 (6.0)</td>
<td></td>
</tr>
<tr>
<td>&gt; 60</td>
<td>2 (0.3)</td>
<td>0 (0)</td>
<td>2 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td>0.920</td>
</tr>
<tr>
<td></td>
<td>174 (24.9)</td>
<td>134 (74.9)</td>
<td>392 (75.2)</td>
<td></td>
</tr>
<tr>
<td>Education status (bachelor's degree)</td>
<td></td>
<td></td>
<td></td>
<td>0.033</td>
</tr>
<tr>
<td></td>
<td>67 (9.6)</td>
<td>23 (12.8)</td>
<td>39 (7.5)</td>
<td></td>
</tr>
<tr>
<td>Position</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manager</td>
<td>233 (33.3)</td>
<td>61 (34.1)</td>
<td>172 (33.0)</td>
<td>0.854</td>
</tr>
<tr>
<td>Full-time EMT</td>
<td>195 (27.9)</td>
<td>68 (38.0)</td>
<td>127 (24.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Paramedic</td>
<td>229 (32.7)</td>
<td>128 (71.5)</td>
<td>343 (65.8)</td>
<td>0.168</td>
</tr>
<tr>
<td>Population of the area</td>
<td></td>
<td></td>
<td></td>
<td>0.070</td>
</tr>
<tr>
<td>0–5,000</td>
<td>100 (14.3)</td>
<td>23 (12.8)</td>
<td>77 (14.8)</td>
<td></td>
</tr>
<tr>
<td>5,001–10,000</td>
<td>175 (25.0)</td>
<td>39 (21.8)</td>
<td>136 (26.1)</td>
<td></td>
</tr>
<tr>
<td>10,001–30,000</td>
<td>143 (20.4)</td>
<td>32 (17.9)</td>
<td>111 (21.3)</td>
<td></td>
</tr>
<tr>
<td>30,001–50,000</td>
<td>32 (4.6)</td>
<td>10 (5.6)</td>
<td>22 (4.2)</td>
<td></td>
</tr>
<tr>
<td>50,001–100,000</td>
<td>43 (6.1)</td>
<td>15 (8.4)</td>
<td>28 (5.4)</td>
<td></td>
</tr>
<tr>
<td>100,001–300,000</td>
<td>131 (18.7)</td>
<td>30 (16.8)</td>
<td>101 (19.4)</td>
<td></td>
</tr>
<tr>
<td>300,001–500,000</td>
<td>20 (2.9)</td>
<td>7 (3.9)</td>
<td>13 (2.5)</td>
<td></td>
</tr>
<tr>
<td>&gt; 500,001</td>
<td>56 (8.0)</td>
<td>23 (12.8)</td>
<td>33 (6.3)</td>
<td></td>
</tr>
<tr>
<td>No. of dispatches per year</td>
<td></td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>0–100</td>
<td>385 (55.0)</td>
<td>78 (43.6)</td>
<td>307 (58.9)</td>
<td></td>
</tr>
<tr>
<td>101–500</td>
<td>182 (26.0)</td>
<td>56 (31.3)</td>
<td>126 (24.2)</td>
<td></td>
</tr>
<tr>
<td>&gt; 501</td>
<td>133 (19.0)</td>
<td>45 (25.1)</td>
<td>88 (16.9)</td>
<td></td>
</tr>
<tr>
<td>Type of facility</td>
<td></td>
<td></td>
<td></td>
<td>0.253</td>
</tr>
<tr>
<td>Head office</td>
<td>25 (3.6)</td>
<td>3 (1.7)</td>
<td>22 (4.2)</td>
<td></td>
</tr>
<tr>
<td>Fire department</td>
<td>564 (80.6)</td>
<td>145 (81.0)</td>
<td>419 (80.4)</td>
<td></td>
</tr>
<tr>
<td>Field office</td>
<td>111 (15.6)</td>
<td>31 (17.3)</td>
<td>80 (15.4)</td>
<td></td>
</tr>
<tr>
<td>Years of doing the same job</td>
<td>12.6 ± 8.0</td>
<td>13.1 ± 8.3</td>
<td>12.5 ± 8.0</td>
<td>0.530</td>
</tr>
<tr>
<td>Shift</td>
<td></td>
<td></td>
<td></td>
<td>0.794</td>
</tr>
<tr>
<td>Only day shift</td>
<td>19 (2.7)</td>
<td>3 (1.7)</td>
<td>16 (3.1)</td>
<td></td>
</tr>
<tr>
<td>Double shift</td>
<td>155 (22.1)</td>
<td>41 (22.9)</td>
<td>114 (21.9)</td>
<td></td>
</tr>
<tr>
<td>Three shifts</td>
<td>130 (18.6)</td>
<td>33 (18.4)</td>
<td>97 (18.6)</td>
<td></td>
</tr>
<tr>
<td>24-hr shift</td>
<td>396 (56.6)</td>
<td>102 (57.0)</td>
<td>294 (56.4)</td>
<td></td>
</tr>
<tr>
<td>No. of night shifts per month</td>
<td>9.8 ± 2.1</td>
<td>10.1 ± 1.7</td>
<td>9.7 ± 2.2</td>
<td>0.013</td>
</tr>
<tr>
<td>No. of hours worked per week</td>
<td>46.3 ± 15.5</td>
<td>48.3 ± 15.6</td>
<td>45.6 ± 15.4</td>
<td>0.051</td>
</tr>
<tr>
<td>Overtime hours per week</td>
<td>2.9 ± 4.1</td>
<td>3.3 ± 4.8</td>
<td>2.7 ± 3.9</td>
<td>0.104</td>
</tr>
<tr>
<td>No. of paid vacations per year</td>
<td>12.7 ± 7.0</td>
<td>12.8 ± 7.4</td>
<td>12.6 ± 6.9</td>
<td>0.621</td>
</tr>
<tr>
<td>Involved in management of COVID-19 patients</td>
<td>604 (86.3)</td>
<td>162 (90.5)</td>
<td>442 (84.8)</td>
<td>0.060</td>
</tr>
<tr>
<td>Degree of burden of responsibility of the EMT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responsibility in determining the medical condition of the patient</td>
<td>83.4 ± 19.1</td>
<td>84.4 ± 19.7</td>
<td>83.1 ± 18.9</td>
<td>0.456</td>
</tr>
<tr>
<td>Responsibility for transporting critically ill patients</td>
<td>89.2 ± 16.8</td>
<td>89.7 ± 18.6</td>
<td>89.1 ± 16.2</td>
<td>0.690</td>
</tr>
<tr>
<td>Responsibility to communicate with physicians</td>
<td>72.4 ± 26.7</td>
<td>76.7 ± 26.7</td>
<td>70.9 ± 26.6</td>
<td>0.013</td>
</tr>
<tr>
<td>BSJQ (supervisor support score)</td>
<td>7.0 ± 2.2</td>
<td>8.1 ± 2.1</td>
<td>6.6 ± 2.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SWING-J (FWNS)</td>
<td>1.2 ± 1.7</td>
<td>1.9 ± 2.1</td>
<td>1.0 ± 1.4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are presented as number (%) or mean ± standard deviation.
FWNS, family-to-work negative spillover; EMT, emergency medical technician; BSJQ, Brief Job Stress Questionnaire; SWING-J, Japanese version of Survey Work–Home Interaction–Nijmegen.
Risk factors for the frequency of burnout among EMTs

The results of a multilevel logistic regression model analysis adjusted for predefined covariates to examine the hypotheses are presented in Table 2. Support from supervisors was an independent factor associated with burnout (OR, 1.426; 95% CI, 1.289–1.577; P < 0.001). The FWNS was also an independent factor associated with the frequency of high-severity burnout (OR, 1.268; 95% CI, 1.138–1.413; P < 0.001). There was no statistically significant association between burnout and the burden of responsibility associated with communication with physicians (OR, 1.007; 95% CI, 0.999–1.015; P = 0.085).

DISCUSSION

The results showed that, contrary to the hypothesis, burnout among EMTs was not associated with the burden of responsibility associated with communication with physicians involved in transporting patients who required emergency care. The independent risk factors for burnout among EMTs were associated with less support from supervisors and FWNS. Therefore, measures that improve support from supervisors and enhance work-life balance are required.

There was no association between burnout among EMTs and the burden of responsibility associated with communication with physicians. There are several possible explanations for this lack of an association. In Japan, the prehospital care system has strengthened to expand the scope of medical practice for EMTs, and the enhanced collaboration between physicians and EMTs may not have been associated with burnout [42]. Communication between prehospital and hospital healthcare professionals is essential for high-quality patient care [43]. The information EMTs obtain from patients includes current medical history, history of illness, family information, and advanced care planning. These are valuable sources of information to improve in-hospital care. Many studies have been conducted on enhancing the communication skills of EMTs, and their strategies have been examined [44]. In Japan, the strategic implementation of communication training in education for EMTs and in clinical settings may have had a negative association with burnout [42]. Moreover, there is evidence of a normalized perception that EMTs should have responsibility for transporting emergency patients as their training includes working in such emergency situations in prehospital settings. Task shifting is performed in prehospital care for out-of-hospital cardiac arrest, and EMTs are being trained to master more responsible procedures, which may also be related to the results of this study [41].

FWNS causes a high prevalence of burnout among EMTs as an independent risk factor. Among non-EMT healthcare professionals, reducing FWNS is deemed to improve mental and physical well-being [38]. However, we believe that the same is not reported among EMTs. A favorable home environment may increase job satisfaction and correlate with lower turnover intentions [45]. Supervisor support is important to improve FWNS [46], and the study includes this as an independently associated factor. A positive relationship with a supervisor can reduce stress in the work environment and create a more positive self-perception [47]. Staff who have a good relationship with their supervisors are more likely to be trusted by the supervisors and, thus, have a higher level of autonomy [48]. Based on the BJSQ, EMTs are unable to discuss their work and personal matters with their supervisors due to a lack of trust in their supervisors. Therefore, to reduce the prevalence of burnout among EMTs, enhancement of the supervisor-staff relationship is necessary. A teamwork system for healthcare professionals called TeamSTEPPS (Team Strategies and Tools to Enhance Performance and Patient Safety) helps to improve healthcare quality, safety, and efficiency. We recommend the interventions such as team training tools to promote patient safety [49]. Supervisors should address the family needs of their subordinates, provide work flexibility, and empathize with staff [50].

There were several limitations to the current study. First, this study was based on EMTs from a single province in Japan in a limited number of surveys. However, the EMS system and EMT work practices across Japan are the same, presumably with a similar level of burnout. Therefore, we expect this limitation to have a minimal impact on the results. Ideally, however, replication of this study in other parts of Japan for comparisons and generalizations is necessary. Second, the background of EMTs who did not respond to this survey could not be evaluated. Moreover, the differences between the two groups could not be analyzed.

Table 2. Risk factors for the frequency of burnout among EMTs in a multivariate analysis

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Odds ratio</th>
<th>95% Confidence interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>1.043</td>
<td>0.288–3.785</td>
<td>0.948</td>
</tr>
<tr>
<td>Years of doing the same job</td>
<td>1.005</td>
<td>0.975–1.036</td>
<td>0.744</td>
</tr>
<tr>
<td>Paramedic</td>
<td>0.908</td>
<td>0.596–1.383</td>
<td>0.653</td>
</tr>
<tr>
<td>Position</td>
<td>1.134</td>
<td>0.693–1.853</td>
<td>0.617</td>
</tr>
<tr>
<td>24-hr shift</td>
<td>1.129</td>
<td>0.769–1.659</td>
<td>0.535</td>
</tr>
<tr>
<td>Involved in COVID-19 patient management</td>
<td>1.461</td>
<td>0.781–2.733</td>
<td>0.235</td>
</tr>
<tr>
<td>Education status (bachelor’s degrees)</td>
<td>0.593</td>
<td>0.309–1.138</td>
<td>0.116</td>
</tr>
<tr>
<td>Burden of responsibility to communicate with physicians</td>
<td>1.007</td>
<td>0.999–1.015</td>
<td>0.085</td>
</tr>
<tr>
<td>Marital status</td>
<td>1.591</td>
<td>0.986–2.565</td>
<td>0.057</td>
</tr>
<tr>
<td>Full-time emergency medical technician</td>
<td>2.043</td>
<td>1.234–3.383</td>
<td>0.006</td>
</tr>
<tr>
<td>Family-to-work negative spillover</td>
<td>1.264</td>
<td>1.136–1.406</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Low supervisor support</td>
<td>1.421</td>
<td>1.265–1.571</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
web-based questionnaire in this study had a 20% response rate, and some EMTs who refused to participate in the study may have included those who experienced burnout. However, in a previous study on burnout among EMTs, the response rate was similar to that in this study. That study had a similar prevalence of burnout. Therefore, this limitation might not have had a significant impact on this study’s findings.

In conclusion, this study found that supervisor support and FWNS were independently associated with a high frequency of burnout among EMTs. To reduce burnout, enhancing the support from supervisors and facilitating a balance between work and family are important.

ETHICS STATEMENT

This study was approved by a suitably constituted Ethics Committee of Sapporo Medical University (No. 2-1-76) and conformed to the provisions of the Declaration of Helsinki. Informed consent was obtained from all the respondents prior to the survey.

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: JH, SU, YT, SM, SN, HI; Data curation: JH, SU, YT; Formal analysis: all authors; Visualization: JH, SU; Writing—original draft: JH, SU; Writing—review & editing: all authors. All authors read and approved the final manuscript.

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Influence of supervisor support on EMT burnout


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The impact of patient sex on survival after unintentional trauma in Korea: a retrospective, observational, case-control study

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²Department of Information Statistics, Kangwon National University, Chuncheon, Korea

Objective This study aimed to describe the relationship between sex and survival in patients experiencing unintentional trauma.

Methods This retrospective, national population-based observational, case-control study involved a cohort of Korean trauma patients who were transferred to an emergency department by a Korean emergency medical service from January 1 to December 31, 2018. Propensity score matching was used. The primary outcome was survival until hospital discharge.

Results Of 25,743 patients with severe unintentional trauma, 17,771 were male and 7,972 were female. Prior to propensity score matching, there was no significant difference in survival among male and female patients (92.6% vs. 93.1%, P = 0.105). After using propensity score matching to adjust for confounders, there was still no sex difference in survival (male, 93.6% vs. female, 93.1%; P = 0.270).

Conclusion Survival after severe trauma was not influenced by the sex of the patient. Further studies with patients of reproductive age and a larger study population are needed to analyze the effects of sex on survival in patients with trauma.

Keywords Sex; Wounds and injuries; Survival; Propensity score

What is already known
The effect of estrogen on survival of trauma patients has been reported in rodent research. However, studies assessing this effect in humans have produced conflicting results.

What is new in the current study
This study initially attempted to show an increased survival rate in female patients with trauma compared to that in male patients. However, after analysis, sex was not an independent predictor of survival after trauma. Further research should be conducted in patients of reproductive age to investigate the effect of estrogen on survival in specific age groups.
INTRODUCTION

Trauma is a major cause of death worldwide. More than five million people die every year due to trauma [1]. Therefore, many researchers have attempted to develop treatment guidelines for trauma patients. Several investigators have recently focused on the effect of the patient's sex on survival after trauma; however, these efforts have produced conflicting results. Some researchers have argued that estrogen is associated with more favorable outcomes in terms of survival due to its protective effect [2,3]. Studies in rodents have indicated estrogen has beneficial effects in multiple tissues after trauma: estrogen reduces cerebral edema and neuronal degeneration in the central nervous system [4], alters the expression of heat shock proteins in the cardiovascular system [5], reduces the pulmonary inflammatory response to severe blood loss [6], and reduces renal ischemia-perfusion injuries [7]. One study argued that female sex was associated with a lower intensive care unit (ICU) admission rate in those aged 16 to 44 years [8]. Another study reported that female trauma patients had a significantly lower risk of in-hospital mortality compared to male patients, an association that was most apparent in patients younger than 50 years of age [9]. Moreover, another study reported that women of reproductive age had better organ function after traumatic injury or hemorrhagic shock than men of corresponding age [10]. A study conducted in a regional trauma center reported that the patient's sex was independently associated with death after major trauma [11,12].

As the potentially beneficial effect of being female by birth on survival of severely injured patients has not yet been firmly established, a nationwide Korean population-based study was performed to investigate the associations between sex and survival outcomes among severely injured patients. We hypothesized that female patients with trauma would have a lower mortality rate.

METHODS

Ethics statement

The study was approved by the Institutional Review Board of Kyung Hee University Hospital at Gangdong (No. 2022-05-056). The requirement for informed consent was waived due to the retrospective nature of the study.

Study design and setting

This was a retrospective study conducted in Korea, based on the 2018 Community-based Severe Trauma Survey, which was compiled and released by the Korea Disease Control and Prevention Agency (KDCA) with the approval of Statistics Korea in 2019 [13]. Data were collected from patients who experienced severe or multiple trauma and were transported by the Korean emergency medical services (EMS) to a hospital between January and December 2018. The Korean EMS is a government-provided system headed by the National Emergency Management Agency in Korea, which is responsible for providing advanced cardiovascular life support (ACLS) and basic life support (BLS) systems throughout the 17 provincial headquarters. All ambulances are equipped with automated external defibrillators (AEDs) and two or three emergency medical technicians (EMTs) who can administer intravenous fluids and undertake advanced airway management, including endotracheal intubation. Moreover, Korea has a unique trauma center system that divides medical centers by profession and severity of the disease: regional trauma, regional emergency, and local emergency centers. Also, trauma patient transfer guidelines for EMS have been developed to ensure the patient is transported to the correct level of emergency center.

Data collection and process

The Community-based Severe Trauma Survey was constructed based on the medical records of hospitals that were previously associated with the Korea National Fire Agency (NFA) and underwent a nonidentification procedure based on the Korean Personal Information Protection Act and the Statistics Act. A community-based investigator visited the medical institutions to double-check the credibility of the medical records. The data were verified by the KDCA. The survey items included demographic and injury information, progress after initiating medical involvement, and outcomes after hospitalization [13].

The Revised Trauma Score (RTS) and Injury Severity Score (ISS) were used to quantify the severity of trauma. RTS is considered a convenient tool for trauma triage, especially in prehospital settings. This score is based on the patients' Glasgow Coma Scale (GCS), systolic blood pressure, and respiratory rate. The RTS results ranged from 0 to 12, with a score of 12 recorded for patients with normal vital signs [14]. In the prehospital phase, the EMTs evaluated and collected patient information. If the collected data included any of systolic blood pressure less than 90 mmHg, respiration rate less than 10 or more than 29 breaths/min, or abnormal consciousness, the RTS score was automatically less than 12. After gathering information relating to the RTS score, the EMS provider determined the severity of trauma based on the collected data.

The ISS is another widely used scale suitable for use during the hospital phase to evaluate patients with trauma [15]. The ISS is based on the Abbreviated Injury Scale (AIS), which divides the body into six parts (head, face, chest, abdomen, limb, and external), and each part is assigned a severity score ranging from 0 (no
damage) to 5 (severe damage). The sum of the three highest scores among the six parts was used to calculate the ISS score [16].

An ISS score greater than or equal to 16 was generally considered to represent severe trauma. Patients who initially had abnormal RTS values and ISS scores greater than 16, as analyzed by the healthcare providers in the hospital following their arrival, were considered for inclusion in our study analyses.

Data regarding injuries and outcome parameters among male and female patients were collected from the trauma registry. Injury was categorized by severity, ISS, and mechanism of injury (transportation incidents, falls, other, or unknown).

Other covariables were age, elapsed time from call to patient transfers to the site by the EMS, hospital class (regional trauma center, regional emergency center, local emergency center; later simplified to trauma center and nontrauma center), and interventions performed. The Korean government designed a national trauma system in 2012, under which national trauma centers were created to efficiently provide medical care for patients with major trauma.

The study data were divided into three categories: (1) initial disposition plan in an emergency department (such as survival to discharge, survival to transfer, survival to admission, and death after CPR); (2) final outcome after hospitalization (survival or death); and (3) final outcome after emergency department (ED) visit (survival or death). We analyzed the data for patients who transferred to a second hospital in a similar manner.

**Statistical analysis**

The median and interquartile range were calculated for continuous variables, and numbers and percentages were calculated for categorical variables. The patients were divided into two groups (male and female at birth). To compare the two groups, the Mann-Whitney test was used for continuous variables, and the chi-square test was used for categorical variables. Since patient age, ISS, and the elapsed time between the emergency line (119) call to site arrival variables did not follow a normal distribution, a nonparametric test was used. To eliminate the effect of confounding variables that may influence outcome variables, when analyzing basic characteristics, a propensity score matching (PSM) method was used to collect data for both groups. Exact matching was used to match male patients 1:1 with female patients according to propensity score. Using matched data, differences between male and female variables were reanalyzed.

All statistical analyses were performed using R ver. 4.2.3 (R Foundation for Statistical Computing). P-values were based on a two-sided significance level of 0.05.

![Fig. 1. Inclusion and exclusion flowchart. ED, emergency department; OHCA, out-of-hospital cardiac arrest; DOA, dead on arrival; RTS, Revised Trauma Score.](image-url)
RESULTS

A total of 52,262 patients were transported to EDs by EMS in Korea in 2018. A total of 6,018 patients with unknown RTSs (such as dead on arrival or out-of-hospital cardiac arrest [OHCA]), 10,235 patients with RTS of 12 or who had missing data, and 10,266 patients with intentional injury were excluded. Finally, 25,743 patients, comprising 17,771 men and 7,972 women, were considered to have experienced an unintentional traumatic injury. Patient matching was achieved for 61.9% (15,944 of 25,743), comprising 44.9% of men (7,972 of 17,771) and 100% of women (7,972 of 7,972) (Fig. 1).

The male patients were significantly younger than the female patients (52 years [range, 33–64 years] vs. 58 years [range, 36–74 years], P < 0.001). The median ISS was higher in male patients than in female patients (5 [range, 1–13] vs. 4 [range, 1–10], P < 0.001). A greater percentage of male trauma patients tended to be admitted to regional trauma centers or regional emergency centers than of female patients. The elapsed time between the 119-emergency call and EMS arrival at the hospital was shorter for male patients than for female patients (27 minutes [range, 19–40 minutes] vs. 26 minutes [range, 19–38 minutes], P < 0.001). The mechanisms of injury differed between sexes as well. Transportation incidents and falls were the second most frequent causes of trauma in both sexes; however, transportation accidents were more frequent in men than in women (46.7% vs. 42.8%, P < 0.001) (Table 1).

No differences in survival after admission were found between the two groups of patients; however, the clinical plans implement-
Impact of sex on survival of unintentional trauma

ferred patients, there was no sex differences in overall admissions and ICU admissions after transfer to a second hospital. Of 1,793 male patients transferred to another hospital for whom data were available, 96 survived to discharge from the ED and 1,597 (89.1%) were admitted. Among the 1,597 male patients admitted to hospital, 1,432 (89.7%) survived to discharge. In contrast, of the 658 female patients transferred to another hospital for whom data were available, 34 (5.2%) survived to discharge from the ED and 573 (87.1%) were admitted. Among the 573 female patients admitted to hospital, 500 (87.3%) survived to discharge. As a result, a significantly greater percentage of men (1,528 of 1,793, 85.2%) than women (534 of 658, 81.2%) survived (P = 0.047) (Table 3).

Total survival comprised patients who survived in the initial hospital and those who survived in a transfer hospital. In summary, 14,094 male patients (79.3%) and 6,612 female patients (82.9%) who were treated only at the initial hospital survived, and 1,528 male patients (85.2%) and 534 female patients (81.2%) who were transferred to another hospital survived. Overall, 15,622 of 16,879 male patients (92.6%) and 7,146 of 7,673 female patients (93.1%) survived (P = 0.105). No sex difference was observed in survival of trauma patients, including the results after transfer to a second hospital (Table 3 and Figs. 2, 3).

To control for factors other than patient sex that might have influenced their survival after traumatic injury, PSM was conducted. No differences between male and female patients were found

### Table 3. Comparisons of survival rate after admission and after transfer to other hospitals among traumatic patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men (n = 1,793)</th>
<th>Women (n = 658)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome in the ED upon transfer to a second hospital</td>
<td>0.265</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival to discharge</td>
<td>96 (5.4)</td>
<td>34 (5.2)</td>
<td></td>
</tr>
<tr>
<td>Survival to transfer</td>
<td>68 (3.8)</td>
<td>34 (5.2)</td>
<td></td>
</tr>
<tr>
<td>Survival to admission</td>
<td>1,597 (89.1)</td>
<td>573 (87.1)</td>
<td></td>
</tr>
<tr>
<td>Died after CPR</td>
<td>32 (1.8)</td>
<td>17 (2.6)</td>
<td></td>
</tr>
<tr>
<td>ICU admission upon transfer to a second hospital</td>
<td>0.260</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome after admission upon transfer to a second hospital</td>
<td>0.114</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival</td>
<td>1,432 (89.7)</td>
<td>500 (87.3)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>165 (10.3)</td>
<td>73 (12.7)</td>
<td></td>
</tr>
<tr>
<td>Outcome after transfer</td>
<td>0.047</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival</td>
<td>1,528 (85.2)</td>
<td>534 (81.2)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>197 (11.0)</td>
<td>90 (13.7)</td>
<td></td>
</tr>
<tr>
<td>Transfer to other institution</td>
<td>68 (3.8)</td>
<td>34 (5.2)</td>
<td></td>
</tr>
<tr>
<td>Overall outcome</td>
<td>0.105</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival</td>
<td>15,622 (92.6)</td>
<td>7,146 (93.1)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>1,257 (7.4)</td>
<td>527 (6.9)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number (%).

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

*Admitted to the hospital, 1,597 men and 573 women.

Total results include the results in the ED disposition of primary hospital, after admission of primary hospital, and transferred hospital (16,879 men and 7,673 women).

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Fig. 2. Flowchart for male trauma patients. ED, emergency department; CPR, cardiopulmonary resuscitation.
with respect to age, ISS, elapsed time from the 119-emergency call to site to patient transport to the hospital by the EMS, level of care at transfer hospital, and injury mechanism (Table 4).

No differences in intervention rate or survival after admission were found between groups with matched data. However, the clinical plans implemented in the emergency departments were different for male and female patients. A greater percentage of male than female patients was admitted to the ICU (20.1% vs. 18.2%, P = 0.003). Moreover, a greater percentage of female patients was treated at the primary hospital and either discharged or discharged to another institution (Fig. 3).

Table 4. Basic characteristics of trauma patients at emergency departments after propensity score matching (n=15,944)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men (n= 7,972)</th>
<th>Women (n= 7,972)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>57 (38–69)</td>
<td>58 (36–74)</td>
<td>0.148</td>
</tr>
<tr>
<td>Injury Severity Score</td>
<td>4 (1–10)</td>
<td>4 (1–10)</td>
<td>0.503</td>
</tr>
<tr>
<td>Time from the 119-emergency call to site arrival (min)</td>
<td>26 (19–38)</td>
<td>26 (19–38)</td>
<td>0.779</td>
</tr>
<tr>
<td>Hospital class</td>
<td></td>
<td></td>
<td>0.239</td>
</tr>
<tr>
<td>Regional trauma center</td>
<td>1,574 (19.7)</td>
<td>1,614 (20.2)</td>
<td></td>
</tr>
<tr>
<td>Regional emergency center</td>
<td>1,641 (20.6)</td>
<td>1,671 (21.0)</td>
<td></td>
</tr>
<tr>
<td>Local emergency center</td>
<td>3,456 (43.4)</td>
<td>3,478 (43.6)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>1,301 (16.3)</td>
<td>1,209 (15.2)</td>
<td></td>
</tr>
<tr>
<td>Mechanism of injury</td>
<td></td>
<td></td>
<td>0.255</td>
</tr>
<tr>
<td>Transportation incident</td>
<td>3,390 (42.5)</td>
<td>3,410 (42.8)</td>
<td></td>
</tr>
<tr>
<td>Fall</td>
<td>3,327 (41.7)</td>
<td>3,358 (42.1)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1,114 (14.0)</td>
<td>1,042 (13.1)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>141 (1.8)</td>
<td>162 (2.0)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range) or number (%).

Table 5. Comparison of trauma patient outcomes after propensity score matching (n=15,944)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men (n= 7,972)</th>
<th>Women (n= 7,972)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery or TAE performed</td>
<td>1,500 (18.8)</td>
<td>1,563 (19.6)</td>
<td>0.205</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>3,625 (45.5)</td>
<td>3,688 (46.3)</td>
<td></td>
</tr>
<tr>
<td>Survival to transfer</td>
<td>1,112 (13.9)</td>
<td>919 (11.5)</td>
<td></td>
</tr>
<tr>
<td>Survival to admission</td>
<td>3,103 (38.9)</td>
<td>3,264 (40.9)</td>
<td></td>
</tr>
<tr>
<td>Died after CPR</td>
<td>95 (1.2)</td>
<td>97 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>37 (0.5)</td>
<td>4 (0.1)</td>
<td></td>
</tr>
<tr>
<td>ICU admission</td>
<td>1,600 (20.1)</td>
<td>1,452 (18.2)</td>
<td>0.003</td>
</tr>
<tr>
<td>Outcome after admission&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>0.300</td>
</tr>
<tr>
<td>Survival</td>
<td>2,804 (90.4)</td>
<td>2,924 (89.6)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>299 (9.6)</td>
<td>340 (10.4)</td>
<td></td>
</tr>
<tr>
<td>Outcome after ED admission&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Survival</td>
<td>6,429 (80.6)</td>
<td>6,612 (82.9)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>394 (4.9)</td>
<td>437 (5.5)</td>
<td></td>
</tr>
<tr>
<td>Transfer to other institution</td>
<td>1,112 (13.9)</td>
<td>919 (11.5)</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>37 (0.5)</td>
<td>4 (0.1)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number (%).

TAE, transcatheter arterial embolization; ED, emergency department; CPR, cardiopulmonary resuscitation; ICU, intensive care unit.

<sup>a</sup>Admitted to the hospital, 3,103 men and 3,264 women.
**Table 6. Comparison of trauma patient outcome after transfer after propensity score matching**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men (n = 778)</th>
<th>Women (n = 658)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome in the ED upon transfer to a second hospital</td>
<td>0.362</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival to discharge</td>
<td>49 (6.3)</td>
<td>34 (5.2)</td>
<td></td>
</tr>
<tr>
<td>Survival to transfer</td>
<td>34 (4.4)</td>
<td>34 (5.2)</td>
<td></td>
</tr>
<tr>
<td>Survival to admission</td>
<td>683 (87.8)</td>
<td>573 (87.1)</td>
<td></td>
</tr>
<tr>
<td>Died after CPR</td>
<td>12 (1.5)</td>
<td>17 (2.6)</td>
<td></td>
</tr>
<tr>
<td>ICU admission</td>
<td>370 (54.2)</td>
<td>299 (52.2)</td>
<td>0.481</td>
</tr>
<tr>
<td>Outcome after admission&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.579</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival</td>
<td>603 (88.3)</td>
<td>500 (87.3)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>80 (11.7)</td>
<td>73 (12.7)</td>
<td></td>
</tr>
<tr>
<td>Outcome after transfer</td>
<td>0.418</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival</td>
<td>652 (83.8)</td>
<td>534 (81.2)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>92 (11.8)</td>
<td>90 (13.7)</td>
<td></td>
</tr>
<tr>
<td>Transfer to other institution</td>
<td>34 (4.4)</td>
<td>34 (5.2)</td>
<td></td>
</tr>
<tr>
<td>Overall outcome&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.270</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival</td>
<td>7,081 (93.6)</td>
<td>7,146 (93.1)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>486 (6.4)</td>
<td>500 (6.9)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number (%).

<sup>a</sup>Admitted to the hospital, 683 men and 573 women. <sup>b</sup>Total results include the results in the ED disposition of primary hospital, after admission of primary hospital, and transferred hospital (7,567 men and 7,673 women).

Impact of sex on survival of unintentional trauma

Sex-dependent survival of severely injured patients is an emerging medical issue. Laboratory and clinical data related to this issue have been collected in many different countries; however, to date, most studies of the effect of sex on mortality have been conducted in European countries [2,3,8,11,12,15,17–22]. In a single-center study in China, female patients with severe blunt trauma had significantly lower mortality rates than male patients [23]. Our study is the first nationwide retrospective study in Korea to study the relationship between sex and survival in trauma patients. Our study included data for a large study population that was obtained without restrictions due to the size of the hospital or region.

In this study, no statistically significant survival advantage was evident for either sex. Overall, a significantly lower percentage of women underwent general admission, ICU admission, or surgical or angiographic interventions. However, these findings may have been due to confounders, including trauma severity and age. The female patients had significantly lower ISS values and were older than the male patients; the risks associated with surgical or angiographic interventions might be expected to be greater among the female patients and medical professionals may be hesitant to provide such interventions. Nonetheless, physicians consider many factors other than age and severity of trauma when making treatment decisions. Since the data did not include the thoughts of doctors making certain medical decisions, we only could infer those factors may impact the treatment plans.

After controlling for potential confounders (age, severity of trauma, elapsed time from 119-emergency call to site arrival, level of care at transfer hospital) through PSM, there was no statistically significant difference in the survival of male and female trauma patients in our study. However, male sex was associated with transfer to another institution, and female sex was associated with final medical decision of admittance or discharge in the primary hospital.

In this study, the mean age of the female patients was 53.2 years, and most were postmenopausal. The absence of sex-dependent differences in survival of trauma patients in this study may have been due to the decline in estrogen production in post-menopausal women, as was postulated in many previous studies, but the results of those studies have been equivocal. In one study investigating the relationship between trauma patient sex and mortality, logistic regression failed to identify any such association [17]. However, a study conducted in the Netherlands found that male sex was associated with ICU admission in those aged 16 to 44 years, but this association was not identified in the overall study population [8]. In addition, another study concluded that improvement in multiple organ dysfunction after trauma occurred more frequently in women aged 16 to 44 years than in men of the same age group [10]. Previous studies showed that lower ICU admission rate and higher organ function improvement in women of reproductive age than men, but the result of our studies (women
with median age of 58 years showed no difference in mortality after trauma compared to men) did not show a significant protective effect of estrogen against stressful conditions, such as trauma.

Another possible theory is that the protective effect of estrogen existed only in the premenopausal group. In a rodent study, young female mice (6–8 weeks old) had a more favorable immune response to sepsis, such as increased release of proinflammatory cytokines, than male mice of the same age; however, the opposite relationship between mouse sex and immune response was observed in aged mice (2 years old) with reduced sex hormone levels. Since proinflammatory cytokines are released in trauma, the difference of release level between sexes could cause differences in survival of trauma patients. Similar results have been noted in clinical settings. McLauchlan et al. [18] reviewed patients with a mean age of 66 years who were admitted to the ICU because of abdominal sepsis. They concluded that age and female sex were independent risk factors for higher mortality. Further investigation is needed to subdivide our patient groups by age to assess potential protective effects of estrogen. In our study, such analysis could not be performed due to the skewed population of our data: the premenopausal population was too small to categorize.

It is also possible that estrogen provides protective effects in severe trauma, but this effect likely is minimal. This hypothesis is compatible with that of a meta-analysis conducted in 2015, in which Liu et al. [9] compared the risk of death in women with minor-to-moderate injuries or severe injury. The effects of estrogen may not have been prominent in our study since our outcome of interest was survival, not duration of hospital admission or rate of complications after trauma. Moreover, a rodent study argued that proestrous females had greater survival after trauma, as their circulating blood volumes were greater than those of male rodents during and after trauma-hemorrhage [19]. This difference could be eliminated simply in the hospital setting by proactive transfusion of trauma patients, which is standard therapy in major trauma, especially in the regional trauma center setting.

Another possibility is that the protective effect of estrogen is present for only a brief period after a stressful event. Choi et al. [24] assessed differences in survival among male and female patients after OHCA and concluded that women in the reproductive age group had a better chance of survival than men. Their conclusion is consistent with the findings of Deitch et al. [20] and McKinley et al. [21], who speculated that the initial protective effect of elevated estrogen decreased with time from the initial injury. Therefore, the protective effect may exist only in a brief period that may have ended prior to hospital arrival.

The major difference between animal studies and clinical settings is that humans can verbally explain their symptoms. The decision to admit is determined by a doctor based not only on objective findings, but also on subjective findings. If one sex subjectively expresses more symptoms than the other, it may influence the doctor’s decision to admit. In one study that analyzed the outcomes after mild traumatic brain injury in male and female patients, poor coping style was associated with increased post-concussive symptoms, and this was more prevalent in women than in men [22]. As we collected data addressing survival after ED arrival, the reasons for admission were not available. If one sex was admitted more frequently due to subjective symptoms rather than based on severity of trauma, our data could be misinterpreted.

Since the data we collected represent only one year, this study has some limitations. Among the patients with severe trauma, there were too few of reproductive age to analyze as a separate group. To better evaluate the effect of estrogen on severe trauma, further research should be performed after collecting data for several years. Second, there were missing and excluded data as the study was based on a retrospective analysis. Initially, we excluded 10,266 cases categorized as intentional injury, accidental self-harm, or suicide (Fig. 1). These 10,266 cases accounted for almost 20% of the total data collected; however, given that intentional injury and self-harm may have different traumatic mechanisms than those responsible for nonintentional trauma and were beyond the scope of our interest, we excluded the data.

Moreover, significant data were missing from the records of many transferred patients (Table 3), notably the reasons for transfer. Patients may have been transferred from higher-grade hospitals (i.e., tertiary hospitals) to general hospitals due to a shortage of beds or from a low-grade hospital to a tertiary hospital due to severity of trauma; however, because our collected data did not include this information, the analyzed data may have been biased. These missing data were crucial for interpreting the information presented in Table 5. Men were more frequently transferred from the initial hospital to other institutions, but we could not interpret this finding further due to the lack of information. Last, since some data, such as the RTS and ISS, were provided by the EMTs and medical providers, bias could have occurred.

In conclusion, the survival of severely injured female patients admitted to emergency departments in Korea was not significantly different from that of male trauma patients. Future research should focus on the relationships between the sex of the patient and their estrogen concentrations on survival among trauma patients of reproductive age and on the reasons why trauma patients are transferred to other institutions after arriving at the ED or being admitted.
ETHICS STATEMENT

The study was approved by the Institutional Review Board of Kyung Hee University Hospital at Gangdong (No. 2022-05-056). The requirement for informed consent was waived due to the retrospective nature of the study.

CONFLICT OF INTEREST

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

FUNDING

None.

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AUTHOR CONTRIBUTIONS

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

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REFERENCES

The integrative feedback tool: assessing a novel feedback tool among emergency medicine residents

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Department of Emergency Medicine, Rush University Medical Center, Chicago, IL, USA

Objective Feedback is critical to the growth of learners. However, feedback quality can be variable in practice. Most feedback tools are generic, with few targeting emergency medicine. We created a feedback tool designed for emergency medicine residents, and this study aimed to evaluate the effectiveness of this tool.

Methods This was a single-center, prospective cohort study comparing feedback quality before and after introducing a novel feedback tool. Residents and faculty completed a survey after each shift assessing feedback quality, feedback time, and the number of feedback episodes. Feedback quality was assessed using a composite score from seven questions, which were each scored 1 to 5 points (minimum total score, 7 points; maximum, 35 points). Preintervention and postintervention data were analyzed using a mixed-effects model that took into account the correlation of random effects between study participants.

Results Residents completed 182 surveys and faculty members completed 158 surveys. The use of the tool was associated with improved consistency in the summative score of effective feedback attributes as assessed by residents (P = 0.040) but not by faculty (P = 0.259). However, most of the individual scores for attributes of good feedback did not reach statistical significance. With the tool, residents perceived that faculty spent more time providing feedback (P = 0.040) and that the delivery of feedback was more ongoing throughout the shift (P = 0.020). Faculty felt that the tool allowed for more ongoing feedback (P = 0.002), with no perceived increase in the time spent delivering feedback (P = 0.833).

Conclusion The use of a dedicated tool may help educators provide more meaningful and frequent feedback without impacting the perceived required time needed to provide feedback.

Keywords Feedback; Medical education; Resident education
INTRODUCTION

Feedback is important in all fields and is a critical aspect of medical training. In fact, the Accreditation Council of Graduate Medical Education (ACGME) declares feedback to be an essential and required component of resident training [1]. However, studies have demonstrated that current feedback quality can vary, leaving some learners and faculty dissatisfied with the adequacy of the feedback they receive [2–7]. This can be particularly challenging in the emergency department (ED) setting due to time constraints, frequent interruptions, high patient acuity, and learners at multiple stages of training [8,9].

To be effective, feedback should be goal-oriented, constructive, based on observed activities, and timely [10]. It should also focus on specific elements of performance, address how the task was done, and provide guidance to help learners grow beyond their current competence [11]. It is important as well to consider the relationship between the feedback giver and receiver. Borrowing from the psychological concept of a therapeutic alliance, an "educational alliance" is a conceptual framework that incorporates a mutual understanding of educational goals with an agreement on how to work toward those goals [6]. Learners can engage in reflective conversations to relate their self-assessment with educator observations. An educational alliance is strengthened when these discussions are held regularly and often by individuals who exhibit trust and mutual respect. Learners engaged in these alliances are more likely to use the feedback they receive effectively [8,11–16]. However, in the ED setting, feedback is more commonly delivered at the end of the shift in a summative format, frequently using a Milestones-based checklist [17]. This limits the ability to integrate the feedback or sustain the educational alliance since the learner’s next ED shift is often with a different faculty member [8].

Feedback is not always focused on or formally taught as part of graduate medical education, so clinical faculty may not have significant training in the matter. Furthermore, many faculty may not have the time to prioritize keeping up to date with evolving literature in medical education given their other clinical and administrative commitments [18–22]. This can lead to significant variability in how feedback is delivered and result both in learner dissatisfaction with the quality of feedback provided and missed opportunities for growth and development [23–25].

To address this need, we developed a novel feedback tool (Fig. 1) to guide feedback delivery and allow opportunities for integration into the shift. Using a structured tool, residents could identify their specific learning objectives from a full list modeled after the Emergency Medicine (EM) Milestones [26]. Informed by Kolb’s theory of experiential learning, the residents then receive real-time feedback on specific instances after a patient encounter, alter their practice, and see if any changes they made are effective [8,27,28]. Having the learner choose the specific skills in an organized system, with clearly defined and achievable goals to work on during their shift, may prevent defensive reactions and better facilitate learning [5,23]. This could also allow the learner and faculty member to visually track improvements to enable a more comprehensive summative evaluation at the end of the shift.

Our primary goal was to evaluate the impact of a novel tool on the overall consistency in providing attributes of effective feedback in a cohort of EM residents and faculty. A subgroup analysis was planned to evaluate the consistency with regard to specific attributes of effective feedback. Secondary outcomes included differences in perceived feedback timing (i.e., how long feedback takes) and frequency.

METHODS

Ethics statement

The study was approved by the Institutional Review Board of
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Rush University Medical Center (No. 19031105-IRB01). Informed consent was obtained from all interested participants, and all methodologies and procedures were conducted in line with the Declaration of Helsinki guidelines.

Study setting
This was a single-center, prospective cohort study comparing a composite feedback score before and after a novel feedback tool was introduced. The study was conducted at Rush University Medical Center, a 3-year EM residency program at an urban academic center in Chicago, Illinois, USA, and enrolled 36 EM residents and 38 EM faculty members. All EM resident and faculty physicians were eligible for inclusion in the study (with the exception of the authors), though survey completion was optional. We excluded medical students and non-EM residents. All faculty are trained in EM.

Study design
The preintervention phase occurred from August 24, 2020 to October 8, 2020. During this period, faculty gave residents feedback based on the existing end-of-shift evaluation model used in our department. This consisted of an electronic end-of-shift card, which was informed by the EM Milestones. Feedback was not standardized across faculty, and they had not received any specialized training. During the preintervention time period, residents and faculty completed a survey evaluating their feedback experience after each shift (Supplementary Materials 1, 2). Survey reminders were posted throughout the ED, and individualized emails were sent to resident and faculty physicians before each shift.

We reviewed the literature to identify components of effective feedback and existing feedback-assessment tools. We identified a paucity of existing feedback-assessment tools appropriate for use in this study; therefore, a new tool was created. Based on a thorough review of existing literature, we determined that high-quality feedback should be tangible, goal-referenced, actionable, personalized, timely, ongoing, and consistent [8,10]. We drafted a survey to assess these specific components, with the cumulative summary score of all seven aforementioned elements serving as our primary outcome.

The survey was then piloted and iteratively refined by the authors. Content validity was determined by discussion among attending ED physicians, including an assistant program director, associate dean of the medical college, and core faculty members, which included two individuals with extensive experience publishing and presenting on feedback. Response process validity was determined by piloting the survey on two attending physicians, including one core faculty and one noncore faculty member. The survey included seven questions evaluating the feedback quality (Supplementary Material 1), which were assessed using a Likert scale of 1 (strongly disagree) to 5 points (strongly agree). The consistency in providing attributes of effective feedback (feedback quality) was assessed as a summative score, with a total minimum of 7 points and total maximum of 35 points. The survey also asked about the time spent on feedback (<1, 1–3, 3–5, 5–7, or >7 minutes) and the number of feedback instances per shift (0, 1, 2, 3, 4, or ≥ 5). Study data were collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools. REDCap is a secure, web-based software platform designed to
support data capture for research studies that provides an intuitive interface for validated data capture, audit trails for tracking data manipulation and export procedures, automated export procedures for seamless data downloads to common statistical packages, and procedures for data integration and interoperability with external sources [29].

From August 24, 2020 to October 8, 2020, we trained our residents and faculty on the new feedback tool. Training was 30 minutes in length and covered only the use of the feedback tool. We did not conduct specific training regarding feedback best practices or other faculty development during the entire study time period. Faculty were educated on the use of the feedback tool during a faculty meeting with most faculty present, while residents were educated during their conference day. Any absent resident or faculty member was sent both a video and verbal explanation of the feedback tool. After allowing time for training and uptake, we collected postintervention data from October 15, 2020 to March 19, 2021, using the same process described above for the preintervention period.

Feedback tool
The feedback tool was developed based on EM Milestones ver. 1.0 (Supplementary Material 3) [26]. All milestones were included, and each milestone was split into 10 strata based on the five levels and criteria described in the EM Milestones document. We chose 10 strata to provide a wide berth of options for faculty and residents to rate their skill level. Each milestone had its own separate form and was paper-based to facilitate ease of completion and collection. Because data suggest that feedback may be better received when the message is presented conceptually in a visual manner [30], we used a visual scale to track progress directly (Fig. 1).

Prior to each shift, residents selected two milestones on which to focus for the shift. Blank feedback tool forms were stored in a folder near the resident and faculty workstations. Before seeing patients, residents would circle their self-perceived level for both milestones and have a conversation with the faculty about what they needed to do to get to the next level. Midway through the shift, the resident and faculty would revisit the document to see if progress had been made on each milestone. An "X" was placed on the visual scale to indicate where they thought they were at that point in time, prompting another conversation on opportunities for improvement. At the end of the shift, the resident marked the visual scale with a square to denote where they thought they had ended up. This response was independent of the end-of-shift evaluations completed by attendings, separating this feedback process from the formal evaluation process.

Statistical analysis
A dependent means sample size calculation indicated 140 assessments were needed based on an alpha value of 0.05, power of 80%, and mean total score difference of 1 between the preintervention and postintervention arms. The normality of data was assessed by visual inspection of histogram plots. We report descriptive statistics for the participant responses using median with interquartile range (IQR) values. Preintervention and postintervention data were analyzed using a linear mixed-effects model that took into account the correlation of random effects between study participants and reported as mean estimates with standard deviations. An a priori, two-sided, P-value of < 0.05 was considered statistically significant. Comparative data were reported as differences and 95% confidence interval values. A post hoc Bonferroni correction was completed for the subanalyses and set at P < 0.005 given the use of one model per the 10 strata evaluated (i.e., original alpha value of 0.05 divided by 10). Analyses were performed using IBM SPSS ver. 22.0 (IBM Corp).

RESULTS
Thirty-one residents and 35 faculty participated in the study. In the preintervention period, residents completed 101 total surveys, with a median of four surveys (IQR, 2–6) per person, while faculty completed 94 surveys, with a median of three surveys (IQR, 1–5) per person. In the postintervention period, residents completed 81 total surveys, with a median of two surveys (IQR, 1–4) per person, while faculty completed 64 surveys, with a median of three surveys (IQR, 2–4) per person. Characteristics of the participant groups are noted in Table 1.

The resident data suggested that there was a significant improvement in the composite feedback score after the intervention (linear mixed-model mean estimate, preintervention = 26.6/35.0 vs. postintervention = 28.2/35.0; P = 0.041) (Table 2). Compared to

Table 1. Characteristics of the study population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Presurvey</th>
<th>Postsurvey</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of participants (%)</td>
<td>No. of surveys (%)</td>
</tr>
<tr>
<td>Resident</td>
<td>24 (100)</td>
<td>101 (100)</td>
</tr>
<tr>
<td>Postgraduate year 1</td>
<td>8 (33.3)</td>
<td>32 (31.7)</td>
</tr>
<tr>
<td>Postgraduate year 2</td>
<td>7 (29.2)</td>
<td>28 (27.7)</td>
</tr>
<tr>
<td>Postgraduate year 3</td>
<td>9 (37.5)</td>
<td>41 (40.6)</td>
</tr>
<tr>
<td>Faculty (yr)</td>
<td>28 (100)</td>
<td>94 (100)</td>
</tr>
<tr>
<td>&lt; 5</td>
<td>10 (35.7)</td>
<td>29 (30.9)</td>
</tr>
<tr>
<td>5–10</td>
<td>6 (21.4)</td>
<td>17 (18.1)</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>12 (42.9)</td>
<td>48 (51.1)</td>
</tr>
</tbody>
</table>
before the implementation of the feedback tool, residents perceived that the faculty spent more time providing feedback (preintervention = 3.1/5.0 vs. postintervention = 3.4/5.0, P = 0.036) and that feedback was more ongoing throughout the shift (preintervention = 3.5/5.0 vs. postintervention = 3.9/5.0, P = 0.023).

In the faculty group, the difference in the overall composite feedback score was not statistically significant (preintervention = 26.2/35.0 vs. postintervention = 26.9/35.0, P = 0.259) (Table 3). Faculty felt that the tool led to more ongoing feedback over the course of the shift (preintervention = 3.3/5.0 vs. postintervention = 3.8/5.0, P = 0.002) without a perceived increase in time spent delivering feedback (P = 0.833).

**DISCUSSION**

As medical education continues to advance and new generations of medical learners transform the ways in which they acquire knowledge, it is critical that the ways in which feedback is given to these learners also evolve [31,32]. Using our novel feedback tool, we found significantly increased consistency in the composite score of attributes of effective feedback (feedback quality) without a significant change in time perceived by faculty devoted to delivering feedback.

Prior literature has focused primarily on faculty development sessions to improve feedback delivery, with fewer studies focusing on supporting tools. One study used a training session on delivering feedback (P = 0.833).
feedback delivery paired with a reminder card and booklet for documentation of noted observations and found a modest improvement in written evaluations and improvement in residents’ perception that feedback would impact their clinical practice [33]. Another study used an extensive training session coupled with a skills checklist to be completed in observed encounters and found that these interventions improved how specific the content of feedback was and that direct observation was viewed by residents as a valuable aspect of their training [32]. These studies, however, required dedicated faculty coaching and time commitments for the observations, which may be more challenging to secure in the ED setting [33,34]. Other studies have focused on providing tools that can increase the ease with which resident evaluations can be completed, whether using app-based systems or QR codes; these studies have primarily focused on increasing the number of evaluations completed rather than on the feedback itself [35–38]. While increasing the quantity of feedback may be important, unintended consequences, such as degrading the process into one of “form filling” and “checking boxes,” may occur [39]. Most importantly, many of the studies on feedback interventions and tools were conducted outside the ED environment and were limited by their retrospective or qualitative design, with few prospective case-control studies, further highlighting the need for an ED-specific tool.

We believe there are several unique benefits to our tool. One of the main individual attributes of effective feedback that did reach statistical significance in both the faculty and resident groups was “my feedback was ongoing.” We believe that having an interactive, physical tool available throughout the shift may be a key to navigating the challenge of the busy ED with frequent interruptions. A visible feedback tool allows the learner and facilitator to be reminded of the need to have continued conversations related to resident performance. This tool also allows learners to choose their learning goals as well as to reflect on where they stand and how they are progressing, thereby moving the feedback session from a unilateral delivery of feedback to a bilateral discussion [6]. It also emphasized self-reflection and accountability to the process by using clear anchors and a visual tool. Finally, the tool standardizes the approach to giving feedback, is simple to use, and aligns with the existing Milestones framework while simultaneously necessitating only minimal formal training for residents and faculty.

Interestingly, most of the individual attributes of effective feedback did not reach statistical significance independently. As a subgroup analysis, this study was not powered for the analysis of the specific components; therefore, it is possible that it may have been underpowered to detect a difference in the individual feedback components. Alternatively, while having set goals chosen at the beginning of the shift in general can improve the ability to provide concrete feedback, it becomes challenging when the chosen goals are not addressed during the shift. In order to address this, residents were asked to pick a pair of milestones to discuss during the shift so there was a greater chance of having something relevant to provide feedback on. We did not, however, keep track of which milestones were more likely to be selected, if the milestones were applicable to the shift experience, or if residents were given feedback on the full breadth of milestones. This may have contributed to the lack of statistical significance in certain individual scores of effective feedback. For instance, the individual attribute “my feedback was tangible” relies on having instances during the shift that are applicable to the specific milestone chosen. In the future, it may be beneficial to assign several milestones to each shift to ensure residents have a greater chance of receiving feedback on clinically applicable milestones, which may lead to improvement in the scores of the individual attributes of effective feedback. Additionally, removing some milestones that are better assessed outside of the clinical setting from the pool of possible milestones to give feedback on may improve the relevance and effectiveness of the feedback given.

Overall, the use of an interactive feedback delivery tool improved consistency in attributes of effective feedback without impacting the perceived time to deliver feedback. Many of the individual attributes of effective feedback did not reach clinical significance, and future research is needed to evaluate the validity of this tool in other settings and among different learner groups.

There are several important limitations to consider with this study. First, this was conducted at a single EM residency program, and future studies are needed to assess the external validity of the tool itself as well as the findings on its effects on the cumulative attributes of effective feedback. In the future, it would also be beneficial to directly measure the amount of time required to utilize the tool and provide feedback, as some of the responses to questions regarding ease of use and perceived intrusions on workflow. Additionally, this study was conducted using a pre-post design. While there were no feedback interventions other than the tool performed during this time period and no new faculty hired, it is possible that faculty feedback may have improved over time. Another limitation is that this tool was derived using the prior iteration of the Milestones, which have recently been revised. However, as the intervention focused on the delivery model, rather than the specific Milestone categories, we do not anticipate this to significantly impact the findings. Moreover, responses
were voluntary, and it is possible this may have led to selection bias. Finally, the outcomes assessed the impact on a cumulative feedback score but did not assess the impact on patient care or educational significance. While statistically significant, the clinical difference of a mean total score increase of 1 point is unclear, and future studies should ascertain the threshold of a clinically significant difference. Future studies should also assess this among non-EM specialties using specialty-specific Milestones. Studies should also assess this longitudinally, evaluating for the impact on resident performance and potential implications for remediation and competency-based advancement assessments.

SUPPLEMENTARY MATERIALS

Supplementary Material 1. Resident survey.
Supplementary Material 2. Faculty survey.
Supplementary Material 3. Sample feedback tool.
Supplementary materials are available from https://doi.org/10.15441/ceem.22.395.

ETHICS STATEMENT

The study was approved by the Institutional Review Board of Rush University Medical Center (No. 19031105-IRB01). Informed consent was obtained from all interested participants.

CONFLICT OF INTEREST

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

FUNDING

None.

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AUTHOR CONTRIBUTIONS

Conceptualization: all authors; Data curation: all authors; Formal analysis: GDP; Investigation: all authors; Methodology: all authors; Project administration: all authors; Supervision: KMG, MG; Writing—original draft: all authors; Writing—review & editing: all authors. All authors read and approved the final manuscript.

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REFERENCES

The impact of COVID-19 on mortality in trauma patients undergoing orthopedic surgery: a systematic review and meta-analysis

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Objective The global spread of the COVID-19 pandemic has affected all aspects of medicine, including orthopedic trauma surgery. This study aims to investigate whether COVID-19 patients who underwent orthopedic surgery trauma had a higher risk of postoperative mortality.

Methods ScienceDirect, the Cochrane COVID-19 Study Register, and MEDLINE were searched for original publications. This study adhered to the PPRISMA 2020 statement. The validity of the studies was evaluated using a checklist developed by the Joanna Briggs Institute. Study and participant characteristics, as well as the odds ratio, were extracted from selected publications. Data were analyzed using RevMan ver. 5.4.1.

Results After applying the inclusion and exclusion criteria, 16 articles among 717 total were deemed eligible for analysis. Lower-extremity injuries were the most common condition, and pelvic surgery was the most frequently performed intervention. There were 456 COVID-19 patients (6.12%) and 134 deaths among COVID-19 patients, revealing an increase in mortality (29.38% vs. 5.30%; odds ratio, 7.72; 95% confidence interval, 6.01–9.93; P < 0.001).

Conclusion Among COVID-19 patients who received orthopedic surgery due to trauma, the postoperative death rate increased by 7.72 times.

Keywords Wounds and injuries; Orthopedic procedures; COVID-19; Mortality

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INTRODUCTION

The World Health Organization (WHO) announced the discovery of a new condition, COVID-19, in early February 2020, before declaring a global pandemic in March 2020. The rapid global spread of the causative pathogen, SARS-CoV-2, has caused major changes to human life worldwide. Many countries in the Asia-Pacific region, including Australia, Korea, and Japan, were among the first to respond to the COVID-19 epidemic [1].

During the COVID-19 pandemic, emergency room visits decreased, particularly visits for trauma and surgical intervention in traumatology cases [2,3]. With this reduction in visits, patients more frequently received delayed care during the current pandemic [4]. Previous studies have shown that delaying surgery increases mortality and the risk of postoperative pneumonia in trauma patients [5].

The present study sought to conduct a systematic review and meta-analysis on postoperative mortality in COVID-19–positive and COVID-19–negative patients undergoing orthopedic trauma surgery. The present meta-analysis sought to investigate the odds ratio (OR) of mortality in this patient population by comparing statistics between COVID-19–positive and COVID-19–negative groups. We hypothesized that postoperative COVID-19–positive orthopedic trauma patients would have a higher risk of death than those tested negative for COVID-19.

METHODS

Search strategy and study selection

The protocol of this review was registered in PROSPERO (International Prospective Register of Systematic Reviews) on September 27, 2022 (No. CRD42022359112). In accordance with recent PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) 2020 statement for identifying research through databases and registers, a systematic review of the mortality in orthopedic surgery owing to trauma during the COVID-19 pandemic

![Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 statement flowchart of the search strategy and selection of studies.]
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was performed, as shown in Fig. 1 and Supplementary Material 1 [6]. The phrases “orthopedic” AND “trauma” AND “surgery” AND “COVID-19” were used to search the ScienceDirect and MEDLINE (via PubMed) databases for English-language studies that reported mortality among both COVID-19–positive and COVID-19–negative patients. The literature search was conducted on September 20, 2022. A search using MeSH (Medical Subject Headings) terms was carried out whenever possible using the combination of the search 1 (“orthopedic trauma surgery” [MeSH Terms] OR “orthopedic trauma surgery” [All Fields]) AND search 2 (“COVID-19 [MeSH Terms] OR “COVID-19” [All Fields]) strategies.

Inclusion and exclusion criteria
We included observational studies like cohort, cross-sectional, and case–control studies but excluded review articles. The validity of the papers included in this study was evaluated using a series of inquiries based on a checklist in line with the kind of study created by the Joanna Briggs Institute [7,8], as shown in Supplementary Table 1 [9–23] and Supplementary Table 2 [24]. Articles that did not fit the requirements for inclusion were rejected. The inclusion criteria formulated according to the PICO mnemonic for clinical research questions were as follows: (1) P (patient, population, problem): patients of all ages who underwent orthopedic trauma surgery; (2) I (intervention, prognostic factor, or exposure): COVID-19 infection (positive or negative polymerase chain reaction result); (3) C (comparison or intervention): none; and (4) O (outcome): postoperative mortality.

Data synthesis
If possible, the data synthesis included information on patient mean age, sex, death rate, underlying disease, complications, intervention site, type of surgery, and hospital stay. The data were summarized in Microsoft Excel (Microsoft Corp) after their collection, and RevMan ver. 5.4.1 (Cochrane Collaboration) was used for statistical analysis. We performed planned subgroup analyses for the confounding variables, which included time points of patient outcome measurement (inpatient vs. 30-day follow-up) and age (<60 years vs. >60 years). Publication bias was measured by visual inspection of funnel plots and quantitatively using Egger test [25]. We considered findings significant if P < 0.05. GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) scores were used to evaluate the certainty of the evidence for each outcome [26]. A GRADE summary of the findings in Table 1 was generated using GRADEpro (GradePro Inc.) [27].

RESULTS

During the literature search, 717 studies were discovered. After removing duplicates, 691 studies remained, and 32 potentially relevant studies were chosen for eligibility examination. This meta-analysis included 16 observational studies (10 retrospective cohort studies, five prospective cohort studies, and one cross-sectional study). The majority of patients in these investigations were >60 years old. The study characteristics and postoperative mortality findings are shown in Table 2 [9–24]. The most common injury sites were the hip and femur, followed by other lower-limb sites such as the patella, tibia, ankle, foot, and upper limb. Supplementary Table 3 shows the types of injuries that required orthopedic surgery. Hemiarthroplasty, total hip arthroplasty, unspecified elective minor surgery, and open reduction and internal fixation of the femur were the major surgeries performed.

Five studies [15,18,20,21,24] compared the number of ortho-

<table>
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<tr>
<th>Table 1. GRADE summary of findings</th>
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<tbody>
<tr>
<td><strong>Outcome</strong></td>
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<tr>
<td>Overall mortality</td>
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<tr>
<td>Inpatient postoperative mortality</td>
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<tr>
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<tr>
<td>Postoperative mortality at 30-day follow-up</td>
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<tr>
<td></td>
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<tr>
<td>Postoperative mortality in the patients with a mean age of &gt;60 yr</td>
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<td></td>
</tr>
<tr>
<td>Postoperative mortality in the patients with a mean age of &lt;60 yr</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Venous thromboembolism incidence</td>
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</tbody>
</table>

GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; CI, confidence interval; OR, odds ratio.

<sup>a</sup>The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).<sup>b</sup>One study had a high risk of bias and two studies had moderate risk of bias. The 95% CI crosses the line of no effect and has an insufficient sample to meet the optimal information size criteria.
Table 2. Study characteristics and postoperative mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Study period</th>
<th>Study design</th>
<th>Study location</th>
<th>Age (yr)</th>
<th>Female sex</th>
<th>Intervention location</th>
<th>Covid-19 (+)</th>
<th>Covid-19 (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrzejowski et al. [9]</td>
<td>March 23, 2020–April 22, 2020 (1 mo)</td>
<td>Prospective</td>
<td>UK</td>
<td>60.7 (1–98)</td>
<td>88</td>
<td>Upper limb, hip, lower limb, and other trauma</td>
<td>4 (33.33)</td>
<td>4 (2.66)</td>
</tr>
<tr>
<td>Balakumar et al. [11]</td>
<td>March 26, 2020–May 20, 2020 (56 day)</td>
<td>Prospective</td>
<td>UK</td>
<td>65.0</td>
<td>Not reported</td>
<td>Clavicle, upper limb, hip, lower limb, and other trauma</td>
<td>19 (44.18)</td>
<td>11 (7.53)</td>
</tr>
<tr>
<td>Beaven et al. [10]</td>
<td>March 28, 2020–May 25, 2020 (59 day)</td>
<td>Prospective</td>
<td>UK</td>
<td>83.0 (76–90)</td>
<td>Not reported</td>
<td>Proximal femur</td>
<td>9 (22.50)</td>
<td>8 (5.51)</td>
</tr>
<tr>
<td>Clement et al. [12]</td>
<td>March 1, 2020–April 19, 2020 (50 day)</td>
<td>Retrospective</td>
<td>Edinburg, UK</td>
<td>60.0 (14–102)</td>
<td>850</td>
<td>Upper limb, hip, lower limb, and other trauma</td>
<td>22 (32.35)</td>
<td>63 (4.19)</td>
</tr>
<tr>
<td>Dallari et al. [13]</td>
<td>March 8, 2020–May 4, 2020 (58 day)</td>
<td>Retrospective</td>
<td>Italy</td>
<td>83.3</td>
<td>381</td>
<td>Hip</td>
<td>8 (15.09)</td>
<td>5 (1.65)</td>
</tr>
<tr>
<td>Egol et al. [14]</td>
<td>February 1, 2020–April 15, 2020 (75 day)</td>
<td>Retrospective</td>
<td>New York, USA</td>
<td>83.0</td>
<td>78</td>
<td>Hip</td>
<td>6 (35.29)</td>
<td>1 (0.93)</td>
</tr>
<tr>
<td>Fisher et al. [15]</td>
<td>March 16, 2020–May 15, 2020 (61 day)</td>
<td>Retrospective</td>
<td>New York, USA</td>
<td>58.0</td>
<td>10</td>
<td>Not reported</td>
<td>2 (20.0)</td>
<td>1 (4.16)</td>
</tr>
<tr>
<td>Greensmith et al. [24]</td>
<td>March 14, 2020–May 28, 2020 (76 day)</td>
<td>Cross-sectional</td>
<td>UK</td>
<td>81.6 (51–103)</td>
<td>Not reported</td>
<td>Hip</td>
<td>2 (40.0)</td>
<td>5 (5.95)</td>
</tr>
<tr>
<td>Hall et al. [16]</td>
<td>March 1, 2020–April 15, 2020 (46 day)</td>
<td>Retrospective</td>
<td>UK</td>
<td>80.0 (50–101)</td>
<td>Not reported</td>
<td>Hip</td>
<td>9 (36.0)</td>
<td>24 (8.63)</td>
</tr>
<tr>
<td>LeBrun et al. [17]</td>
<td>March 20, 2020–April 24, 2020 (36 day)</td>
<td>Retrospective</td>
<td>New York, USA</td>
<td>85.0 (65–100)</td>
<td>Not reported</td>
<td>Hip</td>
<td>3 (42.85)</td>
<td>7 (2.50)</td>
</tr>
<tr>
<td>Lim et al. [18]</td>
<td>March 1, 2020–May 15, 2020 (76 day)</td>
<td>Retrospective</td>
<td>UK</td>
<td>84.9</td>
<td>70</td>
<td>Neck of femur</td>
<td>1 (14.28)</td>
<td>7 (8.23)</td>
</tr>
<tr>
<td>Pass et al. [19]</td>
<td>July 1, 2020–December 31, 2020 (6 mo)</td>
<td>Retrospective</td>
<td>Germany, Austria, and Switzerland</td>
<td>85.0 (80–89)</td>
<td>2,678</td>
<td>Proximal femur</td>
<td>32 (26.01)</td>
<td>214 (5.90)</td>
</tr>
<tr>
<td>Sobti et al. [20]</td>
<td>March 1, 2020–May 31, 2020 (3 mo)</td>
<td>Prospective</td>
<td>UK</td>
<td>83.5</td>
<td>Not reported</td>
<td>Neck of femur</td>
<td>3 (50.0)</td>
<td>5 (10.63)</td>
</tr>
<tr>
<td>Thakrar et al. [21]</td>
<td>March 15, 2020–April 15, 2020 (1 mo)</td>
<td>Retrospective</td>
<td>UK</td>
<td>81.6 (54–100)</td>
<td>Not reported</td>
<td>Hip</td>
<td>4 (33.0)</td>
<td>1 (16.60)</td>
</tr>
<tr>
<td>Zajonz et al. [23]</td>
<td>January 1, 2020–January 31, 2021 (1 yr)</td>
<td>Retrospective</td>
<td>Germany</td>
<td>82.0</td>
<td>219</td>
<td>Proximal femur</td>
<td>5 (41.67)</td>
<td>12 (6.53)</td>
</tr>
</tbody>
</table>

Values are presented as mean (range), number only, or number (%).
Table 3. Incidence of venous thromboembolism, underlying disease, complications, and length of hospital stay in COVID-19–positive and COVID-19–negative groups

<table>
<thead>
<tr>
<th>Study</th>
<th>Total post-operative mortality</th>
<th>Primary cause of postoperative death</th>
<th>Underlying disease</th>
<th>Complication</th>
<th>Primary cause of postoperative death</th>
<th>Underlying disease</th>
<th>Complication</th>
<th>Venous thromboembolism incidence</th>
<th>Mean hospital stay (day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrzejkowski et al. [9]</td>
<td>8</td>
<td>4 Complications due to COVID-19</td>
<td>1 COPD</td>
<td>Not reported</td>
<td>1 Pneumonia</td>
<td>1 COPD</td>
<td>Not reported</td>
<td>COVID-19 (+)</td>
<td>COVID-19 (-)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 Diabetes</td>
<td></td>
<td>1 t-ICH</td>
<td>2 Diabetes</td>
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<td>Not reported</td>
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<td></td>
<td></td>
<td></td>
<td>1 Lung cancer</td>
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<td>1 Sepsis</td>
<td>1 Lung cancer</td>
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<td>Not reported</td>
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<tr>
<td></td>
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<td></td>
<td>1 Autoimmune disease</td>
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<td>Not reported</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>1 Prostate cancer</td>
<td></td>
<td></td>
<td>1 Hypothyroidism</td>
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<td>Not reported</td>
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<td></td>
<td>1 Heart failure</td>
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<td>Not reported</td>
<td>COVID-19 (+)</td>
<td>COVID-19 (-)</td>
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<td>1 Old age</td>
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<td></td>
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<td>1 NOF fracture</td>
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<td>Not reported</td>
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<td>COVID-19 (+)</td>
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<th>Underlying disease</th>
<th>Complication</th>
<th>Venous thromboembolism incidence</th>
<th>Mean hospital stay (day)</th>
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Table 3. (Continued)

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<th>Complication</th>
<th>Primary cause of postoperative death</th>
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<td>7 Cardiac decompensation with myocardial failure</td>
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</table>

COVID-19 (+) | COVID-19 (–) | Venous thromboembolism incidence | Mean hospital stay (day)
| (↑)         | (↓)           |                           |                   |
| 0           | 2             | 15.6                      | 11.5              |

COPD, chronic obstructive pulmonary disease; t-ICH, traumatic intracranial hemorrhage; IHD, ischemic heart disease; CKD, chronic kidney disease; AF, atrial fibrillation; NOF, neck of femur; AHI, acute heart failure; URI, urinary tract infection; ARF, acute renal failure; PE, pulmonary embolism; MI, myocardial infarction; ARDS, acute respiratory distress syndrome; DVT, deep vein thrombosis; UGIB, upper gastrointestinal bleeding; SUI, sepsis of unknown origin; PUD, peptic ulcer disease; GERD, gastroesophageal reflux disease; BPH, benign prostatic hyperplasia; CAD, coronary artery disease; GI, gastrointestinal.

Fig. 2. No publication bias is visible in the funnel plot of the selected studies. This figure displays the qualitatively evaluated asymmetry findings from each study OR odds ratio.

Fig. 3. The forest plot shows the pooled estimates for the outcomes of interest. The size of the squares is proportional to the weight of the study. The horizontal lines represent the 95% confidence intervals (95% CI).

Fig. 4. The forest plot for the subgroup analysis of the pooled estimates. The size of the squares is proportional to the weight of the study. The horizontal lines represent the 95% CI.

Fig. 5. The forest plot for the subgroup analysis of the pooled estimates. The size of the squares is proportional to the weight of the study. The horizontal lines represent the 95% CI.

Fig. 6. The forest plot for the subgroup analysis of the pooled estimates. The size of the squares is proportional to the weight of the study. The horizontal lines represent the 95% CI.
significance among all studies included in our meta-analysis. We analyzed the 16 trials and established a random-effects model, resulting in an overall OR of 7.72 (95% confidence interval [CI], 6.01–9.93; P < 0.001; I² = 0%). The test for subgroup differences in Figs. 4 and 5 [9–24] indicated a statistically significant subgroup effect (P < 0.05) for index hospitalization (OR, 8.67; 95% CI, 5.82–12.91), 30-day follow-up (OR, 7.32; 95% CI, 4.30–12.49), and in patients with a mean age of > 60 years (OR, 7.75; 95% CI, 6.02–9.97). Mortality in COVID-19–positive patients with a mean age of < 60 years showed an increase in one study, but this increase was not statistically significant (OR, 5.75; 95% CI, 0.46–72.30; P = 0.18). As shown in Fig. 6 [13–15,17,23], the incidence of venous thromboembolism (VTE) was increased among COVID-19–positive patients (OR, 4.08; 95% CI, 1.23–13.58). According to these findings, COVID-19 positivity might increase the mortality rate and occurrence of thromboembolism in patients undergoing orthopedic surgery.
DISCUSSION

This systematic review and meta-analysis looked at the death rate among COVID-19–positive and COVID-19–negative trauma patients undergoing orthopedic surgery. Most of the participants in this study were > 60 years old. This finding is consistent with those of Atinga et al. [28], who found that geriatric trauma cases are increasing every year and now account for > 25% of all significant trauma cases in the United Kingdom. Aging is associated with progressive physiological changes that affect various systems. Elderly people respond to trauma in a physiologically different manner than other people. Physiological responses in the elderly might vary due to co-occurring diseases, premorbid frailty, and prescribed drugs.

Previous research has linked hip fracture in the elderly to greater morbidity, a loss of autonomy in activities of daily living, a high rate of institutionalization, and mortality. Conservatively, mortality after hip fracture surgery is high in the first year, being approximately 30% of all cases [29–31]. In this study, 70 of the 134 patients with postoperative deaths among 456 COVID-19–positive patients who underwent orthopedic surgery had a hip or femur fracture.

According to Supplementary Table 4, the most commonly performed procedure in this study was hip arthroplasty. Haskel et al. [32] discovered that hip fracture volume in the elderly did not decrease during the lockdown period, even in areas severely af-

### Table A

<table>
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<tr>
<th>Study or Subgroup</th>
<th>COVID-19 + Events</th>
<th>Total</th>
<th>COVID-19 - Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
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<td>146</td>
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<td>Beaven et al. [10]</td>
<td>22</td>
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<td>63</td>
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<td>10.92 [8.19, 19.29]</td>
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<td>Clement et al. [12]</td>
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<td>424</td>
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<td>57.92 [8.37, 525.04]</td>
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<td>5</td>
<td>5</td>
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<td>1.8%</td>
<td>10.53 [1.42, 78.18]</td>
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<td>Greensmith et al. [24]</td>
<td>9</td>
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<td>279</td>
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<td>5.95 [2.38, 14.90]</td>
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<td>29.25 [2.43, 351.43]</td>
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<td>12.63 [3.61, 44.24]</td>
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<tr>
<td>Total (95% CI)</td>
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<td>6972</td>
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<td>7.75 [6.02, 9.97]</td>
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### Table B

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<th>Total</th>
<th>Weight</th>
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<td>24</td>
<td>100.0%</td>
<td>5.75 [0.46, 72.30]</td>
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<tr>
<td>Total (95% CI)</td>
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<td>24</td>
<td>100.0%</td>
<td>5.75 [0.46, 72.30]</td>
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**Fig. 5.** Postoperative mortality in the patients with a mean age of (A) >60 years and (B) <60 years. M-H, Mantel-Haenszel test; Random, random-effects model; CI, confidence interval.

**Fig. 6.** Occurrence of venous thromboembolism in COVID-19–positive and COVID-19–negative groups. M-H, Mantel-Haenszel test; Random, random-effects model; CI, confidence interval.
fected by COVID–19 outbreaks. Age, a large waist circumference, a lower skeletal muscle index, bone mass density, vitamin D level, physical function, nutritional status, and cognitive function are linked to hip fractures in the elderly [33,34].

VTE involves both pulmonary embolism and deep vein thrombosis, respectively, and occurs in 0.6% to 1.5% of patients undergoing total joint arthroplasty. The risk factors for VTE are described by Virchow triad, which are venous stasis, endothelial damage, and a hypercoagulable state. VTE is typically the result of the interaction of two or less causes. Venous stasis can occur both during and after surgery due to intraoperative immobilization. Prolonged immobility raises the possibility of VTE development [35].

Previous research found that COVID–19–positive patients had a higher mortality rate during hip and femur fracture surgery [36–39]. Surgery within 48 hours of hospital admission does not correlate with a lower mortality rate in COVID–19–positive patients [13]. As shown in Table 3 [9–24], the mean hospital stay length among COVID–19–positive patients undergoing hip and femur surgery was longer than that among COVID–19–negative patients. This result is in line with the study by Kayani et al. [37], which stated that hip surgery in COVID–19–positive patients was associated with a longer hospital stay, longer immobilization, more hospitalizations in the intensive care unit, an increased chance of peri–operative complications, and greater mortality rates. COVID–19–positive patients with a smoking history and multiple (> 3) significant comorbidities have a higher risk of death. Identifying factors that contribute to a higher death rate may improve prognostic classification and interdisciplinary perioperative care.

This review has some limitations. The majority GRADE rating in Table 1 was low because the evidence came from observational studies. Inaccurate studies with smaller sample sizes of COVID–19–positive patients may be influenced by chance. Of the 16 studies, only nine provided information about the type of surgery performed, eight reported the primary cause of postoperative death, and just one provided information about the type of anesthesia used in both groups. All of the included studies were conducted prior to the availability of COVID–19 vaccines.

In conclusion, the postoperative mortality rate among COVID–19–positive patients was 7.72 times greater than that of COVID–19–negative patients. Identifying risk factors for increased mortality may improve prognostic classification and interdisciplinary perioperative management. The findings of this study should be considered by the larger orthopedic community when developing guidelines for treating orthopedic trauma in specific populations in the COVID–19 era.

SUPPLEMENTARY MATERIALS

Supplementary Table 1. Joanna Briggs Institute risk of bias quality assessment for cohort studies
Supplementary Table 2. Joanna Briggs Institute risk of bias quality assessment for cross-sectional studies
Supplementary Table 3. Indications for orthopedic surgery during the COVID–19 pandemic
Supplementary Table 4. The reported surgery in this study
Supplementary Material 1. PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) checklist.
Supplementary materials are available at https://doi.org/10.15441/ceem.22.403.

ETHICS STATEMENT

Not applicable.

CONFLICT OF INTEREST

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

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AUTHOR CONTRIBUTIONS

Conceptualization: HDP; Formal analysis: VH, RP; Methodology: all authors; Project administration: HDP; Writing–original draft: HDP; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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Use of clinical phenotypes to characterize emergency department patients administered intravenous opioids for acute pain

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Objective Individual experience with opioids is highly variable. Some patients with acute pain do not experience pain relief with opioids, and many report no euphoria or dysphoric reactions. In this study, we describe the clinical phenotypes of patients who receive intravenous opioids.

Methods This was an emergency department-based study in which we enrolled patients who received an intravenous opioid. We collected 0 to 10 pain scores prior to opioid administration and 15 minutes after. We also used 0 to 10 instruments to determine how high and how much euphoria the patient felt after receipt of the opioid. Using a cutoff point of ≥50% improvement in pain and the median score on the high and euphoria scales, we assigned each participant to one of the following clinical phenotypes: pain relief with feeling high or euphoria, pain relief without feeling high or euphoria, inadequate relief with feeling high or euphoria, and inadequate relief without feeling high or euphoria.

Results A total of 713 patients were enrolled, 409 (57%) of whom reported not feeling high, and 465 (65%) reported no feeling of euphoria. Median percent improvement in pain was 37.5% (interquartile range, 12.5%–60.0%). One hundred seventy-eight participants (25%) were classified as experiencing pain relief with euphoria or feeling high, 190 (27%) experienced inadequate relief with euphoria or feeling high, 101 (14%) experienced pain relief without euphoria or feeling high, and 244 (34%) reported inadequate relief without euphoria or feeling high.

Conclusion Among patients who receive intravenous opioids in the emergency department, the experiences of pain relief and euphoria are highly variable. For many, pain relief is independent of feeling high.

Keywords Opioid analgesics; Morphine; Hydromorphone; Euphoria; High
INTRODUCTION

Individual experience with opioids is highly variable. Some patients do not experience pain relief when administered therapeutic doses of intravenous (IV) opioids [1–3]. Similarly, emergency department (ED) patients with acute pain exposed to opioids report variable euphoric experiences, with many reporting no euphoria or dysphoric reactions [4–6].

For emergency physicians, use of parenteral opioids has become fraught. Increasing awareness of the long-term sequelae of opioid exposure impacts the risk-benefit calculation even though most opioid-naive patients exposed to opioids in the ED will not transition to opioid use disorder [7–10]. It is important to understand which patients exposed to opioids in the ED are at risk of this transition. Unfortunately, instruments such as the Opioid Risk Tool, which have some utility in the outpatient setting, have proved ineffectual among ED patients [8,11].

More work is needed to understand which ED patients exposed to opioids are at risk of poor long-term outcomes. To further this goal, we delineated four clinical phenotypes: (1) pain relief with feeling high or euphoria; (2) pain relief without feeling high or euphoria; (3) inadequate relief with feeling high or euphoria; and (4) inadequate relief without feeling high or euphoria. Presumably, patients who are administered IV opioids and experience pain relief with euphoria or feeling high are at highest risk of transition to opioid use disorder. Those who experience pain relief without euphoria or feeling high may be the most suitable for opioid use.

In this study, we assigned clinical phenotypes to ED patients with pain who received IV opioids using standardized scales to measure pain relief and euphoria shortly after exposure to the opioids. These clinical phenotypes can potentially be used in subsequent studies to predict risk of transition to opioid use disorder.

METHODS

Ethics statement
The study was approved by the Institutional Review Board of Albert Einstein College of Medicine (No. 2019-10482). All participants provided written informed consent for publication of the research details.

Study design and setting
Data were obtained from an observational study designed to determine the risk of persistent opioid use among ED patients with severe pain who received IV opioids. The goal of our analysis was to define clinical phenotypes based on two axes: pain relief and feeling high or euphoria. These data were collected between February 2021 and June 2022.

The study was conducted in the two academic EDs of Montefiore Medical Center (Bronx, NY, USA). Research associates staffed the EDs throughout the study period and gathered all outcome data.

Selection of participants
We included any adult patient (≥ 18 years) who presented to the ED with pain of sufficient severity that the initial treatment was an IV opioid. We excluded patients who did not have the capacity to understand the consent process in English or Spanish or if they refused to participate. Neither type nor dose of IV opioid was standardized for this protocol—this was left to the clinical team and based on perceived need, typical practice, and clinician experience.

Measurements
All data were obtained through interview with the study participant, with the exception of type and dose of opioid administered and discharge diagnosis, which were obtained by chart review (study participants would not necessarily have access to these...
data). We asked all participants whether they had used any pain medication (and if yes, which one) in the previous 6 months.

To measure feeling high and euphoria, we relied on instruments originally developed as part of the Addiction Research Center Inventory, a comprehensive questionnaire used to determine the subjective effects of psychoactive substances [12]. The items we used have been validated for use among recreational opioid users [13,14] and refined among ED patients with acute pain [4–6]. For this study, we used a two-item instrument: (1) What was your level of feeling high with the medication? (2) What was your level of euphoria, joy, or happiness with the medication? Responses were recorded on an 11-point integer scale with 0 defined as “none” and 10 as “the highest level imaginable.” We anticipated a fair amount of overlap between feeling high and euphoria, joy, or happiness but we thought some respondents might experience feeling high as a dysphoric experience and some might experience euphoria but would not want to stigmatize the feeling by labeling it as feeling high; thus, we included both items in our interview. Euphoria and feeling high were assessed 15 minutes after the IV opioid was administered so that participants could describe the sensation as it was occurring. Participants were also asked to respond to the following open-ended prompt: “Please describe the effects of the opioid medication.”

Pain intensity was assessed on a validated 11-point integer scale (0, no pain; 10, the worst pain imaginable) commonly used in ED research [15,16]. Pain intensity was assessed before the IV opioid was administered and again 15 minutes later.

Outcomes
The primary outcome was assignment of each participant to one of four clinical phenotypes: (1) pain relief with feeling high or euphoria; (2) pain relief without feeling high or euphoria; (3) inadequate relief with feeling high or euphoria; and (4) inadequate relief without feeling high or euphoria. We report the frequency of each of these clinical phenotypes within our cohort.

Statistical analysis
We report graphically the distribution of scores for “What was your level of feeling high with the medication?” and “What was your level of euphoria, joy, or happiness with the medication?” Because there is no defined cutoff point for these scales (feeling high vs. not and euphoria vs. none), we determined the impact of euphoria or feeling high based on the median response (this turned out to be 0 vs. ≥ 1) versus 5, the middle of the 0 to 10 scale. We also report the concordance between the feeling high and euphoria scores using a cross-tabulation table. Our a priori definition of feeling high or euphoria was a score at or above the median for either of the two items.

We also report the distribution of pain relief scores (baseline pain – 15-minute pain) and the percent improvement calculated using the following formula: (baseline pain – 15-minute pain)/baseline pain. We considered adequate pain relief to be an improvement in pain ≥ 50%. We examined the association between pain relief and feeling high or euphoria using Spearman rho.

We also report feeling high and euphoria scores for all patients who reported use of pain medication in the previous 6 months by type of pain medication.

RESULTS

Characteristics of study subjects
During the 17-month enrollment period, 713 patients were enrolled and provided complete data. Baseline characteristics of the cohort are depicted in Table 1. Of the cohort, 679 (95%) received morphine and 34 (5%) received hydromorphone. The median morphine dose was 4 mg (interquartile range [IQR], 4–4 mg), the median hydromorphone dose was 2 mg (IQR, 1–2 mg).

Main results
Of the 713 participants, 409 (57%) reported feeling high score of 0, and 465 (65%) reported a euphoria score of 0 (Fig. 1A, B). The

<table>
<thead>
<tr>
<th>Table 1. Baseline characteristics</th>
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<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Diagnostic grouping</td>
</tr>
<tr>
<td>Nonspecific abdominal pain</td>
</tr>
<tr>
<td>Kidney stone</td>
</tr>
<tr>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Musculoskeletal (not including back pain)</td>
</tr>
<tr>
<td>Gynecological</td>
</tr>
<tr>
<td>Biliary</td>
</tr>
<tr>
<td>Back pain</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Initial pain score</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>8 or 9</td>
</tr>
<tr>
<td>≤ 7</td>
</tr>
<tr>
<td>Admitted to the inpatient service</td>
</tr>
<tr>
<td>Opioid exposure within the previous 6 months†</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
</tbody>
</table>

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

†Use of oral or parenteral opioids.
median (IQR) score for feeling high was 0 (0–5), and that for euphoria was 0 (0–4). Using score ≥ median on either scale, 368 patients (52%) were categorized as having experienced feeling high or euphoria. When we used the more stringent criteria of score > 5 on either of the 0 to 10 scales, 273 participants (38%) were categorized as having experienced euphoria or feeling high. Agreement between the “feeling high” and “euphoria, joy, or happy” scales is depicted in Table 2.

Median improvement in 0 to 10 pain score between baseline and 15 minutes was 3 (IQR, 1–6). Median pain improvement was 37.5% (IQR, 12.5%–60.0%) (Fig. 1C). Improvement in pain score was associated with feeling high (rho, 0.22; P < 0.01) and euphoria (rho, 0.23; P < 0.01). Median (IQR) pain and euphoria or feeling high scores for each phenotype are reported in Table 3. Impact of the type of opioid received and diagnosis on clinical phenotype is presented in the Supplementary Tables 1 and 2.

The following were the most common descriptors used by patients to describe the effects of opioids: lightheaded or dizziness (n = 147); drowsy, tired, or sleepy (n = 114); good or better (n = 87); relaxed or mellow (n = 38); warm or hot (n = 32); and drugged, drunk, or woozy (n = 8).

Among 260 patients who reported use of any pain medication in the previous 6 months, median (IQR) feeling high and euphoria scores were 0 (0–6) and 0 (0–5), respectively. For 53 patients who reported use of oxycodone within the previous 6 months, median (IQR) for feeling high and euphoria were 0 (0–3) and 0 (0–3), respectively. For 15 patients who reported use of morphine within the previous 6 months, these respective scores were 0 (0–10) and 0 (0–10) and

**Table 2. Cross-tabulation of feeling high versus euphoria, joy, or happiness**

<table>
<thead>
<tr>
<th>Feeling high</th>
<th>Euphoria, joy, or happiness</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1–3</td>
</tr>
<tr>
<td>1–3</td>
<td>4–7</td>
</tr>
<tr>
<td>4–7</td>
<td>8–10</td>
</tr>
<tr>
<td>8–10</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number of participants in each category.

**Table 3. Clinical phenotypes of patients who received opioids in the emergency department**

<table>
<thead>
<tr>
<th>Clinical phenotype</th>
<th>Pain improvement (%</th>
<th>Score (range, 0–10)</th>
<th>Any exposure to opioids during the preceding 6 monthsa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Feeling high</td>
</tr>
<tr>
<td>Pain relief with feeling high or euphoria (n = 178, 25%)</td>
<td>70 (60–100)</td>
<td>5 (2–8)</td>
<td>5 (0–7)</td>
</tr>
<tr>
<td>No pain relief with feeling high or euphoria (n = 190, 27%)</td>
<td>22 (11–33)</td>
<td>5 (2–8)</td>
<td>2 (0–5)</td>
</tr>
<tr>
<td>Pain relief without feeling high or euphoria (n = 101, 14%)</td>
<td>67 (50–90)</td>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
</tr>
<tr>
<td>No pain relief without feeling high or euphoria (n = 244, 34%)</td>
<td>14 (0–30)</td>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range) or number (%).

*Use of oral or parenteral opioids.
DISCUSSION

In this analysis of 713 ED patients who received IV opioids for pain, we found highly variable responses to both pain relief and euphoria or feeling high, with about half of the sample reporting some indication of euphoria or feeling high and about one-third reporting ≥ 50% pain relief. About two-thirds of the sample reported little to no sensations of being high, and a comparable percentage reported no or minimal feelings of euphoria. Only 14% of the sample reported the ideal outcome of pain relief without feeling high or euphoria. Absence of an opioid effect was the most common clinical experience: one-third of the sample reported inadequate pain relief and no feelings of high or euphoria. Other interesting findings include discordance between the reports of levels of feeling high and euphoria, joy, or happiness caused by the medication and the disconnect for many patients between pain relief and euphoria or feeling high.

As evidenced by cross-tabulation, feeling high or feeling joy, happiness, and euphoria are not necessarily the same experience. More than 10% of the sample reported feeling euphoric without feeling high or vice versa, as evidenced by patients who described feeling “drunk,” “groggy,” or “drugged.” Patients who reported feeling euphoric without feeling high may have been reluctant to associate the positive experience with a word that has negative societal connotations.

Our analysis highlights the need for a more patient-centered understanding of opioid-induced euphoria. A one-size-fits-all approach to opioid practice is likely inappropriate for a large number of patients. Many patients may benefit from opioids without substantial risk, while others may be exposed to risk without experiencing notable benefit.

Limitations of this study should be mentioned. First, the scales used to assess pleasurable sensations were initially developed and validated in a nonclinical arena among healthy volunteers and recreational substance users. While these have been used among patients with acute pain in the ED, they scales have not been formally validated in such a setting. Also, these scales are subjective and require open participation. We cannot know if some participants did not answer truthfully due to the perceived stigma associated with feeling high. Furthermore, the order of questions may have influenced participant response to the questions: we asked first about feeling high and then about euphoria, joy, or happiness; finally, we elicited responses with an open-ended question.

By asking about feeling high first, we may have biased subsequent responses.

Furthermore, to assign participants to different phenotypes, we had to choose cutoff points at which to dichotomize the 0 to 10 scales. For the scales for feeling high or euphoria, existing data do not help identify a cutoff point. Fortunately, the median on these scales corresponded to the intuitive cutoff point of 0/1. Thus, patients either experienced some euphoria or feeling of high or none at all. However, this may have resulted in miscategorization of some patients who reported scores of 1 or 2 but really had no meaningful euphoric feelings.

Finally, we did not control or measure how the opioid was administered. A rapid IV push may be associated with a more euphoric experience than a slower IV infusion.

In conclusion, among patients who received IV opioids in the ED, the experience with pain relief and euphoria or feeling high was highly variable. For many patients, pain relief was independent of feeling high or euphoria.

SUPPLEMENTARY MATERIALS

Supplementary Table 1. Clinical phenotype based on opioid received
Supplementary Table 2. Clinical phenotype based on common discharge diagnoses
Supplementary materials are available from https://doi.org/10.15441/ceem.23.018.

ETHICS STATEMENT

The study was approved by the Institutional Review Board of Albert Einstein College of Medicine (No. 2019-10482). All participants provided written informed consent for publication of the research details.

CONFLICT OF INTEREST

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

FUNDING

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AUTHOR CONTRIBUTIONS

Conceptualization: BWF, EI; Methodology: BWF, EI; Data curation: BWF, MT, VA, CG, DJW, EI; Formal analysis: MC, BWF, JS; Validation: BWF, JS; Writing–original draft: MC, BWF; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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Eddie Irizarry  https://orcid.org/0000-0000-0000-0000

REFERENCES

**Supplementary Table 1.** Clinical phenotype based on opioid received

<table>
<thead>
<tr>
<th>Clinical phenotype</th>
<th>Opioid received</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Morphine (n=679)</td>
</tr>
<tr>
<td>Pain relief with feeling high or euphoria</td>
<td>161 (24)</td>
</tr>
<tr>
<td>No pain relief with feeling high or euphoria</td>
<td>183 (27)</td>
</tr>
<tr>
<td>Pain relief without feeling high or euphoria</td>
<td>100 (15)</td>
</tr>
<tr>
<td>No pain relief without feeling high or euphoria</td>
<td>235 (35)</td>
</tr>
</tbody>
</table>

Values are presented as number (%).
**Supplementary Table 2.** Clinical phenotype based on common discharge diagnoses

<table>
<thead>
<tr>
<th>Clinical phenotype</th>
<th>Nonspecific abdominal pain</th>
<th>Kidney stone</th>
<th>Gastrointestinal</th>
<th>Musculoskeletal</th>
<th>Gynecological</th>
<th>Biliary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain relief with feeling high or euphoria</td>
<td>26</td>
<td>37</td>
<td>20</td>
<td>18</td>
<td>25</td>
<td>19</td>
</tr>
<tr>
<td>No pain relief with feeling high or euphoria</td>
<td>26</td>
<td>19</td>
<td>27</td>
<td>27</td>
<td>30</td>
<td>19</td>
</tr>
<tr>
<td>Pain relief without feeling high or euphoria</td>
<td>12</td>
<td>12</td>
<td>24</td>
<td>14</td>
<td>14</td>
<td>32</td>
</tr>
<tr>
<td>No pain relief without feeling high or euphoria</td>
<td>36</td>
<td>32</td>
<td>29</td>
<td>41</td>
<td>31</td>
<td>30</td>
</tr>
</tbody>
</table>
Acute contralateral reexpansion pulmonary edema within a few hours of pleural drainage: a case report

Gi Su Yun¹*, Hong Joon Ahn¹,²*, Changshin Kang¹, Jung Soo Park¹,², Yeonho You¹, Wonjoon Jeong¹, Yong Chul Cho¹

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We report a case of an 83-year-old male patient with massive tuberculous pleural effusion. Percutaneous drainage was performed following a diagnosis of tuberculous pleurisy. Fifteen minutes into the procedure, the patient's condition deteriorated suddenly, necessitating mechanical ventilatory support. A chest radiograph performed after intubation showed partial collapse of the affected lung with pneumothorax. Despite sufficient air drainage and lung expansion, the patient's oxygen demand remained high. A repeat chest radiograph performed 30 minutes after chest tube insertion revealed partial expansion of the affected lung and severe infiltrative patterns in the unaffected lung, suggesting contralateral reexpansion pulmonary edema.

Keywords: Pleural effusion; Thoracentesis; Pneumothorax; Case reports

What is already known
Ipsilateral reexpansion pulmonary edema is well reported to date, however contralateral reexpansion pulmonary edema is uncommon and the pathogenesis involved in the causation is not fully understood.

What is new in the current study
In this report, we presented interesting unusual contralateral reexpansion pulmonary edema.

How to cite this article:

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INTRODUCTION

Reexpansion pulmonary edema (RPE) is a complication of pleural drainage that is frequently encountered after decompression of pneumothorax or pleural effusion. It is a potentially lethal condition, with a reported mortality rate of 20% [1]. Therefore, physicians should consider the possibility of RPE following pleural drainage. Most reported cases involve ipsilateral RPE [2-4]; however, the pathophysiologic mechanism of contralateral RPE remains unclear. We report a case of contralateral RPE after pleural drainage and compare its progression to that of previously reported cases to better understand the pathophysiology of this complication.

CASE REPORT

An 83-year-old male patient who underwent pacemaker implantation for sinus node dysfunction nearly 4 years ago presented to the emergency department with a complaint of dyspnea for 3 days. At presentation, his blood pressure, heart rate, respiratory rate, body temperature, and oxygen saturation were 68 mmHg, 92 beats/min, 30 breaths/min, 36.2 °C, and 93%, respectively. Blood gas analysis showed arterial oxygen tension of 70 mmHg, arterial carbon dioxide tension of 29 mmHg, and blood pH of 7.46. Complete blood count (CBC) analysis revealed a white blood cell (WBC) count, hemoglobin (Hb) level, and platelet count of 7,790/µL, 12.5 g/dL, and 268,000/µL, respectively. Costophrenic angle blunt ing was observed in both hemithoraces on chest radiograph (CXR) (Fig. 1A). We confirmed the presence of a large pleural effusion in the right hemithorax using sonography, whereas there was minimal pleural effusion in the left hemithorax.

Oxygen administered to the patient via a nasal prong helped stabilize the vital signs and relieve dyspnea. Thereafter, diagnostic thoracentesis was performed and revealed lymphocyte predominance and high adenosine deaminase level. A clinical diagnosis of tuberculous pleurisy was established, and antitubercular medication was initiated. Despite good therapeutic compliance, the pleural effusion was not improved. Therefore, percutaneous drainage with a pigtail catheter (8.5 Fr) was performed on hospitalization day 5, and 150 mL of fluid was drained. After approximately 15 minutes, the patient’s condition deteriorated, and his vital signs decreased further. Despite a high-flow nasal cannula, the patient’s respiratory rate was 60 breaths/min; therefore, endotracheal intubation was performed at 45 minutes after percutaneous drainage insertion. A follow-up CXR showed partial collapse of the affected lung with pneumothorax (Fig. 1B).

Although the chest tube drained 1,300 mL of fluid, the patient’s oxygen demand remained high. A repeat CXR was performed and revealed partial expansion of the affected lung and severe infiltrative patterns in the unaffected lung, suggesting contralateral RPE (Fig. 1C). Blood gas analysis showed arterial oxygen tension of 89 mmHg, arterial carbon dioxide tension of 52 mmHg, and blood pH of 7.42 while on a ventilator with 60% oxygen delivery and 10 mmHg of positive end-expiratory pressure. Follow-up CBC analysis showed WBC count of 14,500/µL, Hb level of 11.4 g/dL, and platelet count of 258,000/µL. To avoid exacerbation, the patient was transferred to the intensive care unit. The patient’s oxygenation and fraction of inspired oxygen requirement improved over the next 48 hours. Repeat CBC analysis revealed WBC count of 9,900/µL, Hb level of 11.1 g/dL, and platelet count of 156,000/µL. The patient was successfully extubated, and his CXR revealed an improvement in RPE 2 days after pigtail catheterization (Fig. 1D).

Fig. 1. Serial chest X-rays of our patient from the initial visit to the emergency department. (A) Bilateral pleural effusion on initial chest X-ray examination performed in the emergency department with a definite cannon-ball opacity suggesting unknown metastatic lesion (red arrowheads) and cardiac pacemaker (green arrowheads). (B) Residual pleural effusion and newly occurred pneumothorax (blue arrowheads), as well as an inserted pigtail catheter (black arrowheads) in the affected lung after percutaneous drainage insertion. (C) Contralateral reexpansion pulmonary edema in the left hemithorax approximately 1 hour after chest tube (white arrowheads) insertion into the right hemithorax. (D) Improvement of contralateral reexpansion pulmonary edema 2 days after chest tube insertion.
The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Chungnam National University Hospital (No. 2021-07-098). The need for informed consent was waived as the extracted data included clinical data that did not have any personally identifiable information.

DISCUSSION

Although several studies have reported cases of RPE, its etiopathogenesis is still not fully understood. RPE development might be attributed to a combination of inflammatory responses initiated by lung reinflation and altered hydrostatic forces [1]. This promotes interstitial fluid shift, impairs ventilation, and leads to a clinical syndrome that presents as sudden, dramatic hypoxia that is unresponsive to oxygen supplementation [5].

Her and Mandy [6] suggested that contralateral RPE can be caused by a systemic microvascular injury through a leukocyte-mediated inflammatory reaction. However, the cases considered in their report showed subacute contralateral RPE between 24 and 48 hours after primary drainage of an ipsilateral hemithorax, contrary to the acute onset (within few hours) of contralateral RPE in our case. In addition, leukopenia, which was present in previous cases, was not observed for more than 48 hours after the acute lung injury in our case. Therefore, the hypothesis that contralateral RPE is a leukocyte-mediated acute lung injury was not supported by our findings. Conversely, another case report by Kim et al. [7] reported that contralateral RPE acutely occurred after massive drainage of 1,500 mL; their findings also did not support the theory of leukocyte-mediated contralateral RPE suggested by Her and Mandy [6].

Our case shares several clinical findings with those of Kim et al.[7]’s case. First, acute contralateral RPE occurred within a few hours after primary drainage of the affected lung. Second, the affected lung was not fully expanded due to co-existing pneumothorax and remaining pleural effusion when acute contralateral RPE occurred. Physiologically, net fluid transfer across the pulmonary capillaries depends on the difference between the hydrostatic and colloidal osmotic pressures in the normal physiological state and the permeability of the capillary membrane (Starling’s law) [8]. However, some pathophysiologic states can cause redirection of blood flow to an uninvolved area, increasing the hydrostatic pressure unilaterally and resulting in contralateral pulmonary edema [9]. A previous report stated that an ipsilateral increase in hydrostatic pressure due to jet flow of mitral valve regurgitation can lead to unilateral pulmonary edema [10]; thus, we suggest that contralateral RPE acutely occurring after massive pleural drainage can be caused by acutely increased unilateral hydrostatic pressure rather than by an inflammatory reaction, such as leukocyte-mediated lung injury.

In summary, considering our serial CBC findings and the pathophysiology of unilateral pulmonary edema by ipsilaterally increased hydrostatic pressure, we suggest that the dissymmetric hydrostatic pressure scenario is more suitable in the acute onset of contralateral RPE after massive pulmonary drainage. Further research is required to confirm the pathophysiology of RPE, which can help physicians avoid this emergency in clinical practice.

ETHICS STATEMENT

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Chungnam National University Hospital (No. 2021-07-098). The need for informed consent was waived as the extracted data included clinical data that did not have any personally identifiable information.

CONFLICT OF INTEREST

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

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AUTHOR CONTRIBUTIONS

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Benign discoloration or harbinger of infection: purple urine bag syndrome, a rare urinary phenomenon

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A 56-year-old male patient with a history of prior stroke and recurrent urinary tract infections (UTIs) with suprapubic Foley catheter presented to the emergency department with discolored urine. Physical examination demonstrated intact Foley catheter with the bag containing bright purple urine and yellow urine within the tubing (Figs. 1, 2). Urinalysis was positive for 1+ leukocyte esterase and 26 to 50 white blood cells and numerous bacteria. Urine culture was positive for *Proteus mirabilis* and *Klebsiella pneumoniae*. He was treated with third-generation cephalosporin for presumed UTI. The Foley catheter was not exchanged at this time but presented 2 days later and was noted to be without purple urine.

Purple urine bag syndrome (PUBS) is a discoloration of urine generally seen in patients with UTI. Predisposing patient factors include advanced age, long-term urinary catheterization, chronic kidney disease, increased dietary intake of tryptophan, alkaline urine, concurrent constipation, and ileus [1,2]. Bacteria that are implicated in its development include *Escherichia coli*, *Proteus mirabilis*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* [3]. PUBS is a benign condition that can occur when these gram-negative bacteria in urine convert tryptophan derivatives into pigmented metabolites. The derivative, indoxyl sulfate, is secreted into the urine where the sulfurases and phosphatases convert it into its two metabolites: indigo (a blue pigment) and indirubin (a red pigment) [2]. As these pigments interact with tubing of the Foley bag, a characteristically rare purple hue is produced. While isolated PUBS can be a benign finding, it may be associated with increased patient mortality and should alert the provider to investigate for underlying infection [3].

**What is already known**
Purple urine bag syndrome is a rare urinary finding associated with the biochemical reaction of tryptophan metabolism by urinary bacteria.

**What is new in the current study**
Infrequently seen within the emergency department, it is a rare phenomenon that should be properly identified by the emergency medicine provider and should alert to the possibility of underlying infection.
ETHICS STATEMENT

The patient provided written consent for publication of the research details and clinical images.

CONFLICT OF INTEREST

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

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AUTHOR CONTRIBUTIONS

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A case of full-thickness scalp necrosis with oxidized regenerated cellulose application

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Dear Editor,

Scalp lacerations are a very common injury in the emergency department. The scalp is highly vascularized tissue, and the likelihood of bleeding upon conducting repair procedures is very high. In most cases of lacerations sustained through crushing forces, hemostasis is very difficult to achieve because the wound bed is crushed and bleeding occurs at multiple locations, greatly hindering adequate visualization of the surgical field [1].

The most serious complications following a scalp laceration are uncontrolled bleeding and hematoma formation. Uncontrolled bleeding can delay wound healing and incite wound dehiscence [1]. In contrast, hematomas can threaten the vitality of the overlying skin through tension, delayed wound healing, and increased infection rate. Emergency measures to reduce the incidence of hematoma include rigorous hemostasis, drainage, use of biological glue, padding stitches, and hemostatic compresses such as oxidized regenerated cellulose (ORC) [1,2].

Local and distal vasculature should be assessed carefully. If a wound is actively bleeding, direct digital pressure should be applied for 10 to 15 minutes. Most bleeding from venous sources will stop with properly applied direct pressure [1,3]. If digital pressure alone does not achieve hemostasis, a compression dressing of gauze sponges can be secured with an elastic wrap [1]. This, in combination with elevation, is an effective method of hemostasis.

ORC, such as Surgicel (Ethicon Inc), can be used to control diffuse oozing of blood in wounds left to heal by secondary intention [1]. ORC is a sterile bio-absorbable thrombogenic agent used adjunctively in surgical procedures to assist in the control of capillary, venous, and small arterial hemorrhage when ligation or other conventional methods of control are impractical or ineffective [2,3].

Complications of ORC in acute wounds have not previously been reported. We report a clinical case of postoperative full-thickness skin necrosis following the use of ORC in a scalp laceration.

A 63-year-old woman visited the emergency department having sustained a scalp laceration. The depth of the laceration extended to the periosteum, and local wound exploration showed a crushed subcutaneous layer. Considerable amounts of bleeding and hematoma formation were observed. Rigorous hemostasis was performed by bipolar coagulation and aspiration drainage; however, hemostasis could not be achieved. Prior to skin closure and to prevent hematoma for-
Skin necrosis with oxidized regenerated cellulose

formation, three sheets of hemostatic compresses made of ORC (Surgicel) were applied above the periosteum and left in place. Five days following the procedure, overt necrosis was observed on both sides, drawing the hemostatic compresses to the posterior edge (Fig. 1). Full-thickness necrosis involving the epidermis up to the periosteal layer was observed in the affected region (Fig. 2).

ORC has been used as an absorbable hemostat since World War II [4]. ORC is a sterile bioabsorbable thrombogenic agent used adjunctively in surgical procedures to assist in the control of capillary, venous, and small arterial hemorrhage when ligation or other conventional methods of control are impractical or ineffective. One of the most commonly used ORC is Surgicel. In neurosurgery, instructions for ORC use advise against leaving them in situ in the skull or spine following hemostasis. Indeed, following tumor resection, Surgicel left in situ can induce a granulomatous inflammatory reaction to the foreign body or a chronic, persistent reaction, lasting more than 12 weeks following the procedure, creating a false impression of recurrence upon medical imaging [5]. Elsewhere, ORC use is likely to lead to paralysis or nerve damage when used around the spinal cord or to blindness in case of use in contact with the optic chiasm. Warnings in the packaging describe these risks, stating “by inflating [it], Surgicel can exert an undesirable pressure” that induces nerve injury [5].

In stomatology, leaving ORC under the mucosa has not been reported to induce similar cases of overlying necrosis [6]. In plastic surgery, Skoog used ORC to induce bone formation in the slits palatines, while other authors have demonstrated adverse effects, warning of the potential risks of cyst formation and interference with bone healing [7,8]. Erol has fabricated ORC wrapped with crushed cartilage into a “modeling clay” and used it as a nasal bridge graft for rhinoplasties performed for aesthetic reasons. The author did not report any complications following the use of ORC under the thin skin of the nasal bridge [6]. Oxidized cellulose of vegetable origin, has two active ingredients: soluble uronic acid, which is absorbed within 6 to 18 hours, and a fibrous component, which is phagocytosed by macrophages 48 hours following implantation [9,10]. Its biodegradability leads to a lowering of local pH to a range of 2.5 to 3.0 resulting in a chemical action with bactericidal activity; however, the lower pH can also compromise dermal blood flow [6]. Necrosis of muscle fibers can be observed at ORC implantation sites, likely due to their pH-lowering effects [6,10]. This may explain, in part, how tissue necrosis with a “punch” lesion occurred in this clinical case, where the hemostatic compresses were drawn to the posterior edge of the wound. The mechanical action induced by swelling of oxidized cellulose occurs due to its absorbency (up to 10 times its weight) and can also explain the resulting necrosis. We suggest that this effect was caused by separation of the tissue from the nutrient substrate, in addition to local chemical reactions. It is very likely that the combination of high concentrations of ORC in multiple sheets, left in place following the procedure, induced separation of the overlying tissue from the blood supply that was already rendered fragile by crush injury.

In conclusion, this clinical case raises concerns about the possibility of tissue necrosis following the use of ORC if left in place. Although scalp tissue is rich vascularly, separation of the bleeding skin surface, crushed skin, hematoma, and use of ORC, even in small quantities and without inducing paresthesia, can cause cu-

Fig. 1. Skin necrosis observed 5 days following repair. The patient provided written informed consent for publication of the clinical image.

Fig. 2. Full-thickness necrosis (epidermis to periosteum) observed following removal of sutures for wound exploration. The patient provided written informed consent for publication of the clinical image.
taneous pain as well as necrosis. ORC should be removed immediately once hemostasis is achieved, especially in the case of crushing injuries.

ETHICS STATEMENT

The study was reviewed and approved by the Institutional Review Board of Chungnam National University Sejong Hospital (No. CNUSH 2022-11-015). The patient provided written informed consent for publication of the research details and clinical images.

CONFLICT OF INTEREST

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

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AUTHOR CONTRIBUTIONS

Conceptualization: JHM; Data curation: SKO, YNI; Formal analysis: JHM; Investigation: YHY; Methodology: JSP; Project administration: JHM, SKO, YNI; Resources: WJJ; Software: YCC; Supervision: HJA; Validation: CSK; Visualization: JHM, SKO, YNI; Writing–original draft: JHM; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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REFERENCES

Supraclavicular brachial plexus block: the unsung hero of emergency department regional anesthesia

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Dear Editor,

In the mid-2000s, the supraclavicular brachial plexus (SBP) block surfaced in emergency medicine literature; case reports and series demonstrated it as an effective means for managing challenging upper extremity (UE) injuries [1–4]. Despite its appeal, the SBP block has not gained significant traction in emergency departments (EDs) and is taught rarely in academic emergency medicine curricula. We believe that, though the SBP block is underappreciated, it is extremely valuable and should be learned, taught, and utilized in emergency practice.

One of the main advantages of SBP block is that it is simple to setup. Most brachial plexus blocks involve special equipment not readily accessible in the ED, such as spinal needles, intravenous tubing, and a long linear probe for ultrasound (US). An SBP block, however, only requires a 22-gauge needle, a 20-mL syringe, and a simple short linear probe already included on most US systems. During the procedure, patients can position the UE in adduction as comfortably as possible since no special positioning is required for the procedure. In addition, the SBP block is simple to learn and perform. With the linear probe situated in the supraclavicular fossa, the SBP is visualized on US immediately lateral to the subclavian artery and superior to the first rib and pleura. The shallow position of 1 to 2 cm below the skin surface allows easy accessibility to the SBP [5]. Under US guidance, the physician directs a needle in-plane from lateral to medial toward the SBP and instills local anesthetic within or just outside the sheath (Supplementary Video 1). Injecting at the inferior “corner pocket” nearest the subclavian artery within the SBP sheath guarantees dense anesthesia directly targeting the inferior trunk (Figs. 1, 2) [6,7]. The onset of anesthesia occurs within minutes of injection [6].

To complement its easy learning curve, the SBP block boasts an excellent safety profile. Though pneumothorax is a well-known complication, US guidance has significantly minimized this risk [8–11]. Also, the first rib acts as a backstop to the needle path and may prevent pneumothorax even if the physician advances past the SBP. As with all brachial plexus blocks above the clavicle, hemidiaphragmatic paralysis may persist in up to 70% of patients after an SBP block [12]. However, Renes et al. [13] demonstrated significantly lower rates of hemidiaphragmatic paralysis using less than 20 mL of ropivacaine for a SBP block. Transient hemidiaphragmatic paralysis secondary to phrenic nerve palsy is common after brachial plexus blocks such as the interscalene nerve block, SBP block, and infraclavicular brachial plexus block [14,15]. Yet healthy patients without chronic cardiac or pulmonary disease or obesity tend not to experience respiratory compromise [14], perhaps because the minor respiratory muscles (sternocleidomastoid, scalene, and
intercostals) and contralateral hemidiaphragm compensate. While vascular puncture is also a concern, the subclavian artery lies on the opposite side of the approach, and there are no major arteries in the needle trajectory. Additionally, neuropraxia is a worrisome but relatively infrequent outcome [16]. In a retrospective review performed by Liu et al. [17], 17% of perioperative US-guided SBP blocks involved inadvertent intraneural injection, but no patients suffered brachial plexus injury. Other complications include Horner syndrome and, as with any nerve block, local anesthetic systemic toxicity (LAST). Similar to hemidiaphragmatic paralysis, the risk of LAST can be minimized with lower doses of anesthetic [18].

The SBP block is a safe and powerful technique that enables physicians to anesthetize the entire upper limb including the shoulder in the frequent UE injuries presenting to the ED [5]. There is no equivalent nerve block for the chest, back, or lower extremities. In our ED, for example, we have employed the SBP block for anterior shoulder dislocations; wrist, elbow, and humerus fractures; complicated lacerations; and postoperative compressive neuropathy. Published reports have used it for UE abscesses, fractures, and joint dislocations [1–4]. While other brachial plexus blocks are useful for UE anesthesia, each has its own imperfections. The interscalene block, for example, only anesthetizes the sensory distribution of C5–C7 and excludes the inferior trunk (C8–T1) of the brachial plexus, limiting its use for injuries distal to the elbow. The infraclavicular brachial plexus block, on the other hand, involves a daunting needle trajectory aimed toward the pleura and may also require multiple needle passes. The blind needle path of the retroclavicular approach to the infraclavicular region under the clavicle is followed by a narrow lane between the pleura and the axillary artery, hindering novice users. The axillary nerve block also involves multiple needle passes and requires that the patient abduct the arm, making its impractical for particular injuries.

Musculoskeletal pain is the most common complaint in the ED, and there is no one-size-fits-all technique for management. While the SBP block is not superior to all other brachial plexus blocks, it is underutilized and underutilized in emergency medicine. Considering the ease, safety, and potency of the SBP block, emergency physicians should include the SBP block in the multimodal approach to acute pain.

SUPPLEMENTARY MATERIALS

Supplementary Video 1. Performance of a left-sided supraclavicular brachial plexus block. The left side of the screen is medial; the right side is lateral. With a high-frequency linear probe oriented obliquely in the supraclavicular fossa, the supraclavicular brachial plexus is immediately lateral to the subclavian artery. Supplementary materials are available from https://doi.org/10.15441/ceem.23.035.

ETHICS STATEMENT

Not applicable.

CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Conceptualization: all authors; Project administration: MS; Resources: MS; Supervision: MS; 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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Global prevalence of resuscitation training among the general public: current evidence and future directions

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Dear Editor,

Investigation of international practices in community cardiopulmonary resuscitation (CPR) training constitutes an important area of research, as it may uncover disparities in resuscitation education and inform public health initiatives to improve bystander CPR rates and outcomes after out-of-hospital cardiac arrest. Along with individual population-based surveys carried out around the globe to investigate the prevalence of CPR training among the general public, some systematic research has been undertaken to map and analyze evidence from these observational studies.

A scoping review conducted by our research group [1] was the first study that investigated international evidence from population-based surveys reporting the prevalence of community resuscitation training. Based on 61 published studies conducted in 29 countries, the review showed the following: (1) a lack of data on community CPR training for most countries of the world, (2) a predominance of studies conducted in high-income countries compared to countries with low-income economies, and (3) considerable variation in reported CPR training rates (3%-79%) with a median global prevalence of CPR training amounting to 40% [1]. Alongside this, the scoping review demonstrated significantly higher rates of resuscitation training in countries with higher income economies (50%, 23%, and 17% for high-, upper middle-, and lower middle-income countries, respectively), indicating international disparities in existing practices of community CPR training and suggesting the need to further improve public awareness of cardiac arrest and education on resuscitation worldwide [1].

A recently published systematic review and meta-analysis by Ng et al. [2] corroborated the findings of the aforementioned scoping review [1]. In particular, based on the results of 17 studies, the pooled prevalence of ever been trained in CPR in the general global population was 39.6% (ranging from 3% to 65%), and significant variation was demonstrated for CPR training rates among continents and countries with different gross national income levels (43.6%, 40.1%, and 3.0% for high-, upper middle-, and lower middle-income levels, respectively) [2]. The authors confirmed a positive correlation between national income and the prevalence of community CPR training and concluded that CPR training needed to be promoted among laypersons, particularly in Asia, the Middle East, and low-income regions [2].

While not denying the importance of the research by Ng et al. [2], it is worth noting that the authors neglected to discuss the preceding scoping review [1], while including it in the reference list. The omission of the scoping review results [1] led the authors to overlook some relevant publications, which fit the aim of their systematic review [2], including but not limited to the arti-
articles reporting the prevalence of CPR training based on national population-based surveys conducted in China [3], Poland [4], Korea [5], and Taiwan [6]. This emphasizes the value of a scoping review as a precursor tool that is intended to determine coverage of a body of literature and to provide an overview of studies available on a given topic in order to inform future systematic reviews [7]. The highlighted issue should be regarded as a limitation of the systematic review [2] and remembered to support the scientific rigor and transparency of future studies.

Regarding further research, the results of both reviews suggest that further efforts are needed to develop international best practices for measurement, monitoring, and analysis of community resuscitation training. Besides the general paucity of studies in this area, population-based surveys investigating the prevalence of CPR training among the general public are highly heterogeneous in survey design, methodology, and reporting patterns, which complicates interpretation and comparison of the findings [1]. Hence, development of international Utstein-like consensus guidelines on a standardized survey methodology and reporting of data on CPR training practices seems to be a reasonable way to improve consistency and comparability of future surveys. The availability of such uniform guidance could also encourage resuscitation research in regions of the world where CPR training prevalence is currently unknown, particularly in lower middle- and low-income countries. Reliable research data on CPR education in turn could contribute to the development of interventions seeking to improve public access to resuscitation training, which could contribute to better survival after out-of-hospital cardiac arrest.

ETHICS STATEMENT

Not applicable.

CONFLICT OF INTEREST

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

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REFERENCES

Erratum to “Clinical utilization of four-factor prothrombin complex concentrate: a retrospective single center study”

In the article titled “Clinical utilization of four-factor prothrombin complex concentrate: a retrospective single center study [1],” the labels “Survived” and “Died” were inadvertently reversed in the Fig. 2B pie chart. The correct representation of the data is “Died, 19.1%” and “Survived, 80.9%.” The article has been corrected [1].

REFERENCE