Promoting safety for patients and clinicians
Timely protection of acute MI

**Troponin T**

### Test early
- Troponin test is mandatory for all patients with suspected NSTE-ACS
- An additional 3.3% increase in mortality for every 10 minute delay in treatment
- 18.7% vs 8.4%; NSTEMI vs STEMI 1-year mortality after discharge

### Treat right
- Acute myocardial infarction diagnosis through increase/decrease in Troponin concentration by supplementing clinical symptoms and ECG
- The hsTnT 1h algorithm shortens the reexamination interval of patients suspected of NSTEMI to 1 hour
- Roche hsTnT helps to diagnose AMI more quickly and accurately by providing standardized results

### Save lives
- About 80% of patients AMI Rule in / Rule out within 1 hour
- 43% reduction in risk of in-hospital death when treatment begins within 90 minutes
- Reducing the hospital stay in the emergency room by approximately 40%, improving emergency room congestion and reducing patient waiting time

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**References**
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Patient-reported outcome measures in emergency and acute care: looking beyond the emergency room

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Emergency medical care is a fundamentally important resource across the globe [1]. In the United States alone, more than 130 million visits to the emergency room occurred in 2020, of which 30% were related to injuries and 14% resulted in hospital admissions [2]. The acuity of the condition appropriately directs triage, urgency, resource use, and care intensity [3]. The adage “time is tissue” embodies the philosophy of emergency and acute care: to quickly provide the right care to patients to save their lives. However, mortality and the efficiency with which care is delivered, though incredibly important, should not be the only measures of care quality. Decisions made to treat the medical emergency can have profound short-and long-term consequences for patients, affecting physical function, mental health, well-being, and health-related quality of life.

PROs AND PROMs

Patient-reported outcomes (PROs) are assessments of a patient’s health that come directly from them without interpretation by a healthcare provider or anyone else. PROs are health outcomes that only the patient can know and experience, and for which patients are the most reliable source of information [4]. Examples include physical limitations, symptom burden, emotional distress, and social functioning. Measured with psychometrically sound patient-reported outcome measures (PROMs), PROs translate the patient voice into objective numerical data that can help to align the care provided with outcomes that matter most to patients [5,6].

Incorporating PROMs into clinical care improves patients’ experiences and satisfaction with care, enhances patient-clinician communication, and facilitates shared decision-making [7–10]. For example, Pusic et al. [11] showed that when patients report their PROs daily after ambulatory cancer surgery and receive immediate feedback based on their PROs, patient anxiety decreased. Patients were reassured that what they were experiencing was “as expected,” resulting in fewer phone calls to nurses, reducing nursing workload, and reallocating resources to patients needing nurses most. Beyond reducing unnecessary emergency department use, PROMs can even prolong survival among cancer patients when care teams act on the reported data [11–13]. Perhaps most important, because PROs are the outcomes that matter most to patients, they can help align the care provided with patients’ goals for their care.
In the United States and around the world, PROMs are seeing broader applications in clinical practice, quality improvement, and value-based health care (Fig. 1). For example, the International Consortium for Health Outcomes Measurement (ICHOM) convenes international multidisciplinary working groups of clinical experts and patient advocates to reach consensus on a set of core outcomes that matter most to patients for a particular condition, such as heart failure [14] and colorectal cancer [15]. These standardized core outcome sets include both clinical (e.g., treatment complications, survival) and patient-reported (e.g., urinary function, sexual dysfunction, fatigue) outcomes to provide a comprehensive picture of health outcomes. Other international groups focusing on research and clinical trials, such as the COMET (Core Outcome Measures in Effectiveness Trials) Initiative and the COSMIN (Consensus-based Standards for the Selection of Health Measurement Instruments) Initiative, have also championed consensus-based core outcome sets that include PROMs [16,17]. For example, a core outcome set for out-of-hospital cardiac arrest includes three universal PROMs: the Health Utilities Index Mark 3 (HUI3), Short Form 36-Item Health Survey (SF-36), and EQ-5D-5L [18].

**PROMs IN EMERGENCY AND ACUTE CARE**

Despite these benefits, the clinical application of PROMs to emergency and acute care has been limited to date. One major roadblock is the methodological challenge to ascertain a patient’s baseline status in the emergency room, particularly when a patient is in duress and may not be able to complete PROMs, to allow for comparison. Two strategies have been proposed to circumvent the need to collect PROMs at the time of an emergency event: retrospective PROMs and matched population-based PROMs data.

If patients could accurately recall their pre-emergency health status, retrospective PROMs could serve to establish their baseline health when a pre-emergency measurement is not available. Kwong et al. [19] examined the accuracy of this approach among patients undergoing joint replacement surgery and found intra-class correlation coefficients between 0.61 and 0.80, suggesting high agreement between PROMs completed before surgery and PROMs completed by the same patient after surgery when recalling their presurgery status. They then carried out feasibility studies on patients admitted for two types of emergencies: ST-seg-
ment elevation myocardial infarction managed with percutaneous coronary intervention [20], and gastrointestinal issues treated through laparotomies [21]. Prior to discharge, patients completed PROMs based on recalling their health status 1 month prior to admission. They then completed the same PROMs 3 months after discharge. Though patients were not asked to complete PROMs based upon their current health state at the time of discharge, most patients regained their prior level of recalled health, suggesting that perhaps this retrospective method has potential.

An alternative method for determining the baseline health status of patients who experience unforeseen emergency care involves using PROMs data from similar patients in population surveys as a proxy baseline. Matching patients on demographic characteristics and comorbidities, Kwong et al. [22] also examined this method and found significant discrepancies between the scores from retrospective PROMs and those from the matched patients, indicating that PROMs data obtained from similar patients with similar medical profiles may not serve as a reliable substitute for retrospective PROMs.

These two approaches, retrospective PROMs and matched population-based PROMs data, may be more complicated than necessary. Not all patients will present to the emergency room in extremis, and others are stabilized with treatment. Nowadays, patients have direct access to their medical records through secure mobile applications. Smart health information technology (IT) that recognizes when a patient is in the emergency room could push relevant PROMs to patients to complete while waiting for care or test results. Patients who complete PROMs could be seen faster than others who do not. Indeed, more creative solutions are certainly needed.

However, even without knowing a patient’s baseline health, PROMs can offer valuable insights for tracking long-term trauma outcomes, as shown by the FORTE (Functional Outcomes and Recovery after Trauma Emergencies) project [23,24]. This multicenter study in Boston (MA, USA) used phone interviews at 6- and 12-months posttrauma to collect data using PROMs that are universal (i.e., SF-12) and condition-specific (i.e., Trauma Quality of Life). Despite methodologic limitations, the results showed that many patients had lasting physical and emotional impairments, emphasizing the need for ongoing care. Indeed, efforts to integrate PROMs into trauma care are gaining traction, evidenced by the American College of Surgeons (ACS) Committee on Trauma conference on PROMs, which aimed to workshop existing barriers and to better understand how PROMs can evaluate trauma care quality [25].

More important than when to administer PROMs is choosing the appropriate PROMs with strong measurement properties [6,26,27]. For example, psychometrically sound PROMs tailored for trauma patients are increasingly becoming available, representing a significant step forward. For instance, the LIMB-Q was developed to measure PROs specifically after limb-threatening lower extremity trauma, applicable to patients after either reconstruction or amputation [28]. The LIMB-Q adhered to international guidelines for PROM development and was psychometrically validated using item response theory (IRT) [29]. The application of IRT offers several advantages over classical test theory, such as improved reliability, the ability to handle missing data effectively, and greater precision with shorter assessments [6]. Most importantly, IRT allows for scores to be placed on an interval scale rather than an ordinal one, thus ensuring both the interpretability and clinical relevance of the scores. These attributes make IRT especially suited for clinical care, where quick, accurate, and interpretable evaluations are essential. Nevertheless, there remains an urgent need for more valid and reliable PROMs that are specially designed to address the unique challenges of emergency and acute care environments.

**A BROADER PERSPECTIVE**

Perhaps a broader perspective that looks beyond acute episodes will be needed to achieve the benefits of PROMs in emergency medicine. A robust healthcare system that integrates PROMs into routine care would enable clinicians to use these metrics similarly to vital signs and laboratory values for informed decision-making, ideally in all settings in which the patient can participate. In this universal model, PROMs would be continuously accrued into the electronic health record, allowing for real-time clinical alerts about concerning symptoms, enabling timely interventions [11,12]. It is especially important to track this information during the long periods when the patient is at home, when we typically have little or no interaction with patients. Emergency, ambulatory, and acute care would punctuate this care, and represent a singular point in time along a patient’s entire lifespan.

Achieving this future state is challenging but possible. Large-scale programs to routinely collect PROMs in clinical care are increasing [30], and not only in the United States [31]. For example, Mass General Brigham, an integrated health system in Massachusetts, USA, implemented a standardized PROMs collection program in 2012 [32,33]. Today, more than five million PROMs are completed annually across more than 475 clinics from more than 80 medical, behavioral health, and surgical specialties. Despite these pioneering efforts, more could be done to accelerate
Patient-reported outcomes in emergency medicine

the uptake of PROMs into clinical care. PROMs built with modern measurement theory that can serve multiple purposes, including condition-specific problems and yet retain the ability to compare across diseases, conditions, populations, and systems, need to be developed. These novel, multipurpose PROMs then need to be operationalized by leveraging health IT and interoperability standards [34,35]. PROs data could then "speak a common language" and efficiently track outcomes longitudinally at the individual patient, clinician, community, population, and even global levels.

The fleeting encounter with emergency and acute care makes it challenging to conceptualize how the many promises of PROMs can be applicable. However, the necessary life-saving treatments provided in the emergency setting can result in long-term benefits for patients. Only by measuring PROs can we be confident that patients recover to their baseline, pre-emergency health status to the extent possible. Additionally, innovative PROMs-based solutions in emergency medicine could have a significant, positive impact on patients being treated for mental health issues and alcohol and substance abuse [36]. For now, research into PROMs in emergency medicine remains challenging and needs further work to achieve success. Success, however, may ultimately involve taking a step back from the emergency room to look towards greater healthcare transformation.

ARTICLE INFORMATION

Conflicts of interest

David W. Bates receives grants and personal fees from EarlySense, personal fees from CDI Negev, equity from ValeraHealth, equity from Clew, equity from MDCoin, personal fees and equity from Aesop, personal fees and equity from FeelBetter, personal fees and equity from Guided Clinical Solutions and grants from IBM Watson Health, all outside the submitted work. The authors have no other conflicts of interest to declare.

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REFERENCES


33. Wagle NW. Implementing patient-reported outcome measures. NEJM Catal Innov Care Deliv 2017;3(6).

34. Bates DW, Samal L. Interoperability: what is it, how can we make it work for clinicians, and how should we measure it in the future? Health Serv Res 2018;53:3270–7.


It is well established that the stethoscope is covered in pathogens. Thus, it is recommended that to decrease the population of pathogens that reside on a stethoscope diaphragm, it should be cleaned with at least 60 seconds of alcohol scrubbing before each patient contact [1]. Unfortunately, compliance with these recommendations has never been demonstrated. In fact, the converse is well documented, with recommendation compliant stethoscope hygiene rates rarely exceeding double digits [2,3]. This is because, if performed appropriately before each patient contact, it requires a significant amount of time that could otherwise be dedicated to patient care.

Modeling suggests the time and financial costs associated with clinician's adherence to recommended stethoscope cleaning are not insignificant. This includes the following: (1) the number of auscultating physicians per day in an emergency department (ED); (2) the number of patients seen per clinician; (3) the mean hourly clinician costs; and (4) the hospital compliance rate of stethoscope hygiene. Using an example of a high-acuity area, such as a small 20-bed ED, in which a clinician auscultates an average of 30 times per shift, over three physician shifts per day (90 auscultations per day = 32,850 auscultations per year), with an average annual US emergency physician's salary of USD 352,000 [4], and if observing perfect stethoscope hygiene compliance, results in 547 hours of stethoscope hygiene a year. This is a cost of USD 115,990.40/yr dedicated entirely to clinicians in a single unit for cleaning their stethoscope.

Unfortunately, the reality is that stethoscope hygiene compliance is often much lower than 100%. At a more commonly observed 11% rate of compliance [2,3] physicians would instead be spending 60 hours per year on stethoscope cleaning, at a cost of USD 12,722.89/yr. This model suggests that lower stethoscope hygiene compliance might be cost saving in itself. However, the relationship that lower compliance may lead to higher costs from healthcare-associated infections (HAIs) must be considered.

Methicillin-resistant Staphylococcus aureus (MRSA) and Clostridioides difficile (C. diff) are two examples of pathogens that are commonly found on stethoscope diaphragms [5,6] and US hospital costs of these nosocomial HAIs are estimated to be an average of USD 38,561 per MRSA-related infection [7] and USD 24,205 per C. diff infection [8]. Examining the frequency of pathogen transmission occurrences via the stethoscope diaphragm and their associated costs to the hospital must consider the following: (1) the annual exposure; (2) the likelihood of C diff (5.0%) or MRSA (7.4%) on a clinician’s stethoscope diaphragm [5,6]; (3) the hospital compliance rate of stethoscope hygiene; and (4) the probability of pathogen exposure resulting in an infection. When this model is applied to the previous example of three clinicians each seeing 20 patients a day in the ED, the annual number of auscultations would equal 32,850 patient contacts and would result in 1,642 and 2,431 transmission events of C diff and MRSA, respectively, onto a patient.
Table 1. Cost results based on different infection rates after pathogen exposure in a 20-bed emergency department

<table>
<thead>
<tr>
<th>Infection rate</th>
<th>Clostridiales difficile</th>
<th>MRSA</th>
<th>Total annual cost: lowest possible, USD</th>
<th>highest likely, USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunocompetent (97.3%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1%</td>
<td>16</td>
<td>386,715</td>
<td>24</td>
<td>912,108</td>
</tr>
<tr>
<td>2%</td>
<td>32</td>
<td>773,430</td>
<td>47</td>
<td>1,824,215</td>
</tr>
<tr>
<td>3%</td>
<td>48</td>
<td>1,160,145</td>
<td>71</td>
<td>2,736,323</td>
</tr>
<tr>
<td>Immunocompromised (2.7%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1%</td>
<td>4</td>
<td>107,310</td>
<td>7</td>
<td>253,103</td>
</tr>
<tr>
<td>3%</td>
<td>9</td>
<td>214,621</td>
<td>13</td>
<td>506,206</td>
</tr>
<tr>
<td>1%</td>
<td>13</td>
<td>321,931</td>
<td>20</td>
<td>759,309</td>
</tr>
</tbody>
</table>

MRSA, methicillin-resistant Staphylococcus aureus.

The data to calculate the conversion of exposure rate to infection rate is unknown, as no randomized study has ever consented patients to determine infection rates after pathogen exposure. However, we performed a sensitivity analysis, using an estimate of 2.7% of the population as being immunocompromised [9] with a higher estimated infection rate (ranging from 10% to 30%), and the remaining 97.3% of the population being immunocompetent hospitalized patients with lower infection risks (estimated at 1%–3%). Using C. diff and MRSA exposure parameters, applied to the above population, sustaining infection rates of 1% to 3% for immunocompetent, and 10% to 30% for immunosuppressed, provides a total annual cost estimate of stethoscope hygiene errors that range from USD 1,659,236 to 4,977,708 for C. diff and MRSA, in a single hospital unit (Table 1).

Unfortunately, C. diff and MRSA represent only a small portion of surface pathogens found in the contemporary ED. As reported in the recent pandemic, it must also be considered that the hygiene of stethoscopes may affect the transmission of other pathogens, including respiratory infections such as COVID-19 [10] and influenza. How effectively these pathogens, as well as other infectious diseases (e.g., Ebola), are transmitted by the stethoscope is unknown, but any transmission is likely to increase medical costs.

With the challenges and low success rates of personal stethoscope cleaning, alternatives have been promoted. The single-patient stethoscope is a commonly used strategy. Although less expensive than a HAI resulting from the failure of stethoscope hygiene, it is not cost neutral. For example, a 20-bed ED spending an average of USD 6.00 per single-patient stethoscope on 32,000 patient encounters would be spending USD 192,000 on disposable stethoscopes per year. Secondly, the inferior acoustic qualities of the disposable stethoscope may contribute to actual patient misdiagnosis, with an estimated number needed to harm of 10 [9]. Finally, the sharing of stethoscopes among practitioners, while decreasing pathogen exposure to the patient, has been demonstrated to have concerning rates of pathogens (e.g., Pseudomonas) shared among the clinical staff [11].

Most recently, dispensers of touch free stethoscope barriers have been promoted as elevating stethoscope hygiene to that similar of the gloved hand and providing 100% aseptic patient contact [12]. Their single unit costs are less than 50 cents, and their application time requires less than 2 seconds. When considered in terms of the time compressed requirements of contemporary emergency medicine practice, the ability to save the 1 minute between every patient stethoscope contact by the application of a touch free barrier, rather than the requirement of washing the stethoscope’s diaphragm for 60 seconds with an alcohol swab, suggests the barrier strategy is the optimal guideline compliant intervention. Ultimately, barriers may solve the failures of the unwashed personal stethoscope or the shared disposable stethoscope.

Given the extensive morbidity that occurs with failure to clean the stethoscope, and the fiscal value proposition resulting from the prevention of stethoscope related hospital associated infections, we suggest that improvements in stethoscope hygiene should be supported at the national and regulatory level. This should include the implementation of standardized institutional protocols, as well as support via national subsidies and public funds to insure the implementation and compliance in the use of touch free stethoscope barriers.

ARTICLE INFORMATION

Conflicts of interest

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Data sharing is not applicable as no new data were created or analyzed in this study.

REFERENCES

Blood failure: traumatic hemorrhage and the interconnections between oxygen debt, endotheliopathy, and coagulopathy

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This review explores the concept of “blood failure” in traumatic injury, which arises from the interplay of oxygen debt, the endotheliopathy of trauma (EoT), and acute traumatic coagulopathy (ATC). Traumatic hemorrhage leads to the accumulation of oxygen debt, which can further exacerbate hemorrhage by triggering a cascade of events when severe. Such events include EoT, characterized by endothelial glycocalyx damage, and ATC, involving platelet dysfunction, fibrinogen depletion, and dysregulated fibrinolysis. To manage blood failure effectively, a multifaceted approach is crucial. Damage control resuscitation strategies such as use of permissive hypotension, early hemorrhage control, and aggressive transfusion of blood products including whole blood aim to minimize oxygen debt and promote its repayment while addressing endothelial damage and coagulation. Transfusions of red blood cells, plasma, and platelets, as well as the use of tranexamic acid, play key roles in hemostasis and countering ATC. Whole blood, whether fresh or cold-stored, is emerging as a promising option to address multiple needs in traumatic hemorrhage. This review underscores the intricate relationships between oxygen debt, EoT, and ATC and highlights the importance of comprehensive, integrated strategies in the management of traumatic hemorrhage to prevent blood failure. A multidisciplinary approach is essential to address these interconnected factors effectively and to improve patient outcomes.

Keywords: Hemorrhage; Shock; Coagulopathy; Endotheliopathy; Wounds and injuries
INTRODUCTION

According to the Global Burden of Disease Study 2019 [1], traumatic injury claimed the lives of 2.4 million people around the world and constituted 7.8% of all deaths. Although head injury and hemorrhage are the two most common causes of death from traumatic injury [2], death due to head injury is reported to decrease with the development of the trauma care system and damage control interventions, whereas death due to hemorrhage does not decrease significantly [3]. In addition, although hemorrhage is the most common cause of early trauma death, up to 50% of patients with traumatic hemorrhage can be potentially saved [3,4].

Traumatic hemorrhage is exacerbated by acute traumatic coagulopathy (ATC). In the past, traumatic coagulopathy was attributed to hemodilution from crystalloid fluid resuscitation, along with progressive hypothermia and acidosis, and was considered an unavoidable consequence of resuscitation. However, Brohi et al. [5] reported that clinically relevant ATC may not be related to fluid administration. They found that patients with evidence of ATC on arrival to the emergency department had significantly higher mortality that was positively correlated with the severity of the injury and not the volume of intravenous fluid administered. Another study by Fioccard et al. [6] and Brohi et al. [7] reported that coagulopathy existed at the site of injury in about half the trauma patients managed by mobile intensive care units, and its severity was related to the degrees of injury and hypoperfusion. Thus, if trauma patients experience more severe injuries with significant hemorrhage, hemostasis becomes more challenging. To overcome ATC in severely injured patients, current practices in trauma resuscitation include rapid control of bleeding and maintenance of blood’s hemostatic ability, termed “damage control resuscitation” or “hemostatic resuscitation.” These methods include the use of blood products with very limited use of crystalloid therapy to reduce mortality [8–12].

Timely hemostatic resuscitation using a balanced transfusion ratio of red blood cells (RBCs), plasma, and platelets or whole blood coupled with the use of antifibrinolytic agents such as tranexamic acid has not only improved outcomes, but also decreased inflammatory complications (acute respiratory distress syndrome), number of operations, and the overall amount of used blood products [10]. Thus, hemostatic resuscitation in patients with traumatic hemorrhage appears to give additional protection due in part to its effects on the endothelium, which is injured by hemorrhagic shock [13]. The term “endotheliopathy of trauma (EoT)” was first used by Holcomb and Pati [14] and describes the early damage of the endothelial glycocalyx layer (EGL) after injury. Breakdown of the EGL increases vascular permeability resulting in capillary leakage and exposure of endothelial cells to platelets and white blood cells. These promote thromboinflammation, edema, and organ–barrier dysfunction [15].

ACT and EoT appear to be intricately connected and correlated based on the degree of hypoperfusion. Therefore, this review aims to explore the interconnectedness between these entities.

TRAUMATIC HEMORRHAGE AND OXYGEN DEBT

The relationship between oxygen delivery and oxygen consumption is biphasic (Fig. 1). In a normal resting state, metabolic demand and consumption of oxygen (VO\textsubscript{2}) are independent of oxygen delivery (DO\textsubscript{2}). This steady state of consumption is achieved by tissues extracting larger amounts of oxygen, resulting in hemoglobin leaving organs with lower levels of oxygen saturation. However, when DO\textsubscript{2} decreases below a critical point (critical DO\textsubscript{2}), the levels of oxygen extraction cannot support aerobic metabolism. At this point, major organ systems enter a state of anaerobic metabolism, and an oxygen deficit occurs. Increase of this level (degree of VO\textsubscript{2} below aerobic threshold) over time is the oxygen debt, which can be viewed as whole-body ischemia. Although it is measured precisely in a laboratory setting by indirect calorimetry, oxygen debt can also be reflected clinically (and less precisely) by sequential measures of lactate. Traumatic hemorrhage results in a decrease in DO\textsubscript{2} through decreases in cardiac output and blood oxygen content. Additional factors such as vasoconstriction add to a further reduction in DO\textsubscript{2} to tissues [16,17]. The resulting oxygen debt quantitatively predicts survival and the development of critical DO\textsubscript{2}.
of multiple organ failure after hemorrhage [18–20]. The magnitude of oxygen debt is also linked to levels of mitochondrial dysfunction, oxidative reperfusion injury, and inflammation, leading to necrosis and apoptosis, which contribute to organ dysfunction or failure and even death. The mechanisms of oxygen debt and the resulting cascade of injury also have implications for endothelial damage and coagulation.

Rapid resuscitation from traumatic hemorrhagic shock is critical to not only halt the further accumulation of oxygen debt, but also for its repayment [16]. Failure to repay oxygen debt in a timely manner results in increased reperfusion and inflammatory injury, organ dysfunction, and possible death [21]. However, the ability to ensure repayment is challenging given the biphasic relationship between oxygen delivery and consumption. Stabilizing patients just above critical DO2 will halt anaerobiosis and assist lactate clearance but may not produce the above-baseline levels of VO2 that will result in partial or full repayment. However, early and rapid clearance of lactate appears to be associated with improved chances of oxygen debt repayment.

**BLOOD AS AN ORGAN: DEFINITION OF BLOOD FAILURE**

A body organ is a structural unit consisting of variable cells that work together in coordinated functions. Blood in the circulatory system is enveloped by the endothelium; the vascular endothelium, as a conduit for blood, coordinates the physiological transport of oxygen, carbon dioxide, nutrients, and waste products and connecting physically distant organs. In addition, the endothelium maintains the fluidity of blood by preventing the formation of blood clots through a thromboresistant surface and anticoagulant mediators that function in the endothelium under normal circumstances. Thus, the blood and the endothelium interact intimately, and the blood-endothelial system can be viewed as an individual organ. In this context, it may be considered the largest integrated functional organ system in the body. As such, the blood-endothelial system is a major target of damage from trauma, hemorrhage, hypoperfusion, and reperfusion injury. Traumatic hemorrhage is capable of inducing endothelial dysfunction and damage, which is believed to begin a cascade of ATC [22,23].

It has been suggested that oxygen debt is the main driver behind ATC [5], and reperfusion injury caused by resuscitation may damage fibrinogen and fibrin [24], weakening clots weaker, exacerbating hemorrhage, and worsening oxygen debt. Thus, oxygen debt, endotheliopathy, and ATC are interconnected and are considered collectively as “blood failure” (Fig. 2). Blood failure can be defined as an emergent state of blood that arises during the accumulation of a critical level of oxygen debt.

When oxygen debt occurs, cellular energetic processes change from aerobic to anaerobic metabolism. Normally, oxygen acts as a terminal electron acceptor in the mitochondrial electron transport chain (ETC). Specifically, glucose and fatty acids are metabolized in the cytoplasm and mitochondria, respectively, generating high-energy electron carriers, such as NADH and FADH2. These electron carriers donate their electrons to the ETC, where they pass through a series of protein complexes, including complexes I, II, and III. Finally, at complex IV, molecular oxygen (O2) serves as the final electron acceptor. At this stage, oxygen accepts the electrons donated by the electron carriers and, together with protons (H+) from the mitochondrial matrix, forms water (H2O). This electron transfer reaction allows the flow of electrons to continue within the ETC, producing the proton gradient that drives the synthesis of adenosine triphosphate (ATP) through ATP synthase. The use of oxygen as the terminal electron acceptor in complex IV is crucial for efficient production of ATP, providing the cell with a continuous and robust energy supply to support essential functions. However, under conditions of critically low oxygen delivery, the ETC may leak electrons, leading to the production of reactive oxygen species (ROS). These ROS, including superoxide anion and hydrogen peroxide, can damage cellular components, such as lipids, proteins, and DNA. Electron leaks occur when electrons prematurely escape the ETC and react with oxygen, bypassing complex IV. This uncoupling of electron flow from ATP synthesis disrupts energy production, exacerbates cellular stress, and contributes to mitochondrial dysfunction. In addition, lactate accumulates as a byproduct when the rate of glycolysis exceeds the capacity of oxidative metabolism to utilize pyruvate. This process helps sustain energy production in cells but leads to lactate accumulation, which can decrease pH and exacerbate metabolic acidosis. Moreover, neurovascular compensation through sympathetic activation and catecholamine release activates Na+K+ATPase, increasing lactate production [25] and constricting blood vessels to further reduce blood flow to organs and increase tissue hypoxia. Changes in blood redox potential, accumulation of lactic acid, and an increase of catecholamine resulting from the accumulation of oxygen debt affect endothelial cells and blood components and cause EoT and ATC, which represent blood failure [26–28].

**ENDOTHELIOPATHY OF TRAUMA**

The endothelium is one of the largest parts of the human body,
occupying a blood-endothelial interface measuring approximately 300 to 1,000 m² [29]. The endothelium is formed by a single cell layer and lines all blood and lymphatic vessels. The physiological function of the endothelium includes control of vascular tone, inflammation, angiogenesis, and regulation of coagulation and fibrinolysis [14,30,31]. The endothelial glyocalyx lines the inner surface of the vascular endothelium and consists of membrane-bound proteoglycans, glycoproteins, and soluble plasma or endothelium-derived molecules [32]. When traumatic hemorrhage-induced oxygen debt occurs, it results in hypoxia and catecholamine release. In addition, release of inflammatory mediators and enzymes such as matrix metalloproteinases and heparanases from injured tissue and leukocytes induce shedding of the glyocalyx [22,33,34]. This shedding from the endothelial surface results in loss of barrier function, leading to capillary leaks; exposure of heparan sulfate from endothelial cells, which contributes to coagulopathy through autoheparinization; and release of damage-associated molecular patterns, contributing to systemic inflammation [35–38]. Glyocalyx shedding also exposes the endothelial cell surface and initiates nonspecific adhesion of platelets and leukocytes and generation of thrombin [39,40]. In addition to glyocalyx shedding, ROS and circulating proinflammatory cytokines such as TNF-α and interleukin 6 (IL-6) induce endothelial cells to propagate innate immune responses [41,42]. This shedding of the endothelial glyocalyx and endothelial cell activation result in capillary leaks, nonspecific intravascular coagulation, and inflammation throughout the systemic endothelium of the body. In other words, this is not a localized effect at the site of a traumatic injury.

In clinical studies, shedding of the endothelial glyocalyx is associated with poor outcomes, and increasing plasma levels of the biomarkers syndecan-1, thrombomodulin, hyaluronan, and hepa-
ran sulfate are correlated with the severity of traumatic injury [43–46].

**ACUTE TRAUMATIC COAGULOPATHY**

Coagulopathy after traumatic hemorrhage has long been acknowledged and considered a co-phenomenon and inevitable consequence of large-volume crystalloid resuscitation, hypothermia, and metabolic acidosis. However, endogenous coagulopathy caused by the severity of the traumatic injury itself and the degree of traumatic shock has been recognized and named ATC [5,47]. ATC is a complex and multifactorial condition that begins in the early stages of traumatic hemorrhage and can rapidly progress as levels of oxygen debt increase. Several mechanisms of ATC have been proposed, with additional proposals under investigation. Despite this, it is agreed that ATC involves disturbances in platelet function, fibrinogen depletion, and dysregulated fibrinolysis, leading to impaired blood clotting, excessive bleeding, and potential accumulation of greater oxygen debt.

Platelet dysfunction is a critical aspect of ATC. Trauma-induced shock and tissue injury can activate platelets, causing them to aggregate and release procoagulant substances. However, platelets may also become dysfunctional, leading to decreased clot formation and impaired hemostasis. In a swine traumatic hemorrhage model, it was demonstrated that clot strength is reduced as oxygen debt increases despite unchanged platelet count [48]. In addition, inhibition of platelet function eliminated increases in the firmness of clots in a rat polytrauma model [49]. These findings suggest the importance of platelet function in clot strength, and platelet dysfunction results in weak clots. It has also been reported that platelets from trauma patients show impaired aggregation to ex vivo agonist stimulation independent of platelet count, and this is more pronounced in nonsurvivors [50,51]. Impaired aggregation of platelets was shown to develop very quickly in a porcine model of traumatic hemorrhage and can occur within 15 minutes of injury [52]. The precise mechanism is not known but involves the endothelial release of tissue factor, platelet-activating factor, and von Willebrand factor [53,54], which activates platelets beyond their primary role of hemostasis. This phenomenon is referred to as “platelet exhaustion” [51,55,56]. Circulating soluble factors, which remain undefined, are thought to mediate platelet exhaustion [57], and a platelet transfusion may not necessarily reverse platelet dysfunction [58,59]. In addition to impaired platelet aggregation in patients with traumatic hemorrhage, impairments in the adhesive function of platelets to collagen and contractile force have been reported [60,61]. Platelets with an impaired aggregation response also contribute to tissue plasminogen activator (tPA)-mediated fibrinolysis due to impaired platelet plasminogen activator inhibitor-1 (PAI-1) [62].

Poor survival has been reported in trauma patients with diminished levels of fibrinogen [63]. In a swine model of trauma and hemorrhage, fibrinogen was significantly reduced with increasing oxygen debt [48]. Fibrinogen is converted to fibrin by thrombin and forms a hemostatic plug, together with platelets. It is the terminal substrate for the coagulation cascade and must be maintained at a minimum level for effective hemostasis. The mechanisms for diminished level of fibrinogen in traumatic hemorrhage include impairment of fibrinogen synthesis due to hypothermia, accelerated degradation by acidosis and reperfusion injury, and consumption in clot formation with additional blood loss and hemodilution, further decreasing fibrinogen level [64–66].

Dysregulated fibrinolysis may also be involved in ATC, but the exact mechanism in patients with traumatic hemorrhage remains unclear. Exposure of tissue factors by injury and endothelial disruption activates the extrinsic coagulation pathway and generates thrombin, leading to fibrin and clot formation. Initially, the clotting process is localized at the site of injury, but escape of thrombin from the injury site activates the systemic coagulation process [67]. Normally, thrombin escaped from the injury site is inhibited by circulating antithrombin and thrombomodulin expressed on endothelial cells, and the thrombin–thrombomodulin complex activates protein C to maintain tissue perfusion by inhibiting thrombosis. However, persistent tissue hypoperfusion induces endothelial cell damage, which increases the levels of soluble thrombomodulin and the thrombin–thrombomodulin complex to excessively activate protein C and interfere with blood coagulation [67]. It has been reported that soluble thrombomodulin and activated protein C were increased in trauma patients and are associated with poor clinical outcomes [68]. Although activated protein C is involved in control of fibrinolysis by cleavage of factors Va and VIIIa, as well as binding of PAI-1, and is suggested as a major driver of ATC, the level of activated protein C in trauma patients cannot cleave factor Va efficiently [69]. Rather, hyperfibrinolysis observed in ATC might be associated with the overwhelming systemic release of tissue plasminogen activator from Weibel-Palade bodies stored in endothelial cells and loss of alpha2 antiplasmin and PAI-1 [70–75]. Another concept of dysregulated fibrinolysis is termed “fibrinolysis shutdown” and has been reported as the most common phenotype of dysregulated fibrinolysis in severe trauma patients [76]. Patients who exhibited fibrinolysis shutdown experienced prior hyperfibrinolysis, includ-
ing elevation of D-dimers and depletion of fibrinolytic inhibitors [77]. The mechanism of fibrinolysis shutdown is not fully identified. A surge in PAI-1, shedding of S100A10 plasminogen receptor protein from the surface of endothelial cells that normally drive the hyperfibrinolysis process, and increased level of thrombin-activatable fibrinolysis inhibitor in plasma have been suggested [78–80]. The extent of these processes and level of fibrinolysis are greatest in patients with rapid and massive hemorrhage and reflected in higher oxygen debt [62,76].

CONSIDERATIONS IN THE MANAGEMENT OF BLOOD FAILURE

As indicated above, severe traumatic hemorrhage can result in blood failure, which is collectively composed of oxygen debt, EoT, and ATC. Increasing levels of EoT and ATC will complicate hemostasis, leading to accumulation of greater oxygen debt. To prevent or reverse blood failure in patients with traumatic hemorrhage, immediate control of hemorrhage and repayment of oxygen debt must be combined with simultaneous treatment of both endothelial injury and coagulopathy. Damage control resuscitation (DCR) or hemostatic resuscitation is a strategic approach in patients with severe injuries and hemorrhagic shock. DCR includes immediate control of ongoing hemorrhage, early balanced transfusion of blood products with other hemostatic agents, and permissive hypotension. The combination and simultaneous execution of these strategies reduce the degree of blood failure.

Transfusion of packed RBCs (pRBCs) increases the oxygen-carrying capacity, cardiac output, and thus DO₂. In addition, RBCs influence hemostasis as evidenced by increased accumulation of platelets at a high hematocrit level and the association of increased RBC count with predisposition to thrombosis [81,82]. The proposed mechanisms include increased platelet adhesion and aggregation through the release of adenosine diphosphate and thromboxane A2, the release of membrane-derived procoagulant microvesicles, and aggregation of RBCs with platelets via adhesive molecules [83]. Thus, early use of pRBCs can help to decrease the oxygen debt and provide additional hemostatic effects. There has been concern that pRBCs stored a long period might have altered oxygen affinity and delivery, rheological changes, and adhesiveness to the endothelium, which might affect outcomes [84–86]. However, a recent multicenter, randomized blinded trial did not show any benefit of fresh RBCs in critically ill patients, although most of the patients were not victims of trauma [87,88].

Most guidelines recommend the transfusion of a high ratio of plasma to RBCs, with the majority recommending a 1:1 ratio. Transfusion of plasma increases cardiac output through intravascular volume expansion and supplements coagulation factors to increase hemostatic ability. Additionally, plasma may provide endothelial protection, assisting in recovery of the endothelial glycocalyx, abrogating endothelial hyperpermeability and inflammation, and restoring syndecan-1 expression in the lungs [89–92]. Plasma also promotes homeostasis in thrombin generation [93]. Considering that EoT and ATC develop rapidly after injury, prehospital plasma transfusion may be helpful. Based on this, several militaries have invested in the development and deployment of lyophilized plasma that can be stored, carried, and reconstituted in field environments. However, controversial reports exist on the benefits of prehospital administration of plasma alone on survival and may reflect the need for additional components (pRBCs and platelets) during longer transport times [94,95]. While minor, transfusion of plasma has risks including infectious disease transmission and triggering of transfusion-related acute lung injury [96,97].

Early platelet transfusion in conjunction with pRBCs (1:1 ratio) is associated with improved outcomes in traumatic hemorrhage [98]. Platelets contribute to hemostasis by increasing thrombin formation, clot firmness, and resistance to clot lysis [99]. However, platelets have a limited shelf-life, compromising immediate availability. Platelets are traditionally stored at room temperature to maintain function, but storage is usually limited to 5 days due to growth of bacterial contaminants. However, evidence suggests that storage of platelets at 4 °C may extend the effective lifespan for up to 14 days and may decrease the risk of infectious complications [100–102]. Although cold-stored platelets remain in circulation for a shorter period, they showed better hemostatic function and greater capacity to inhibit endothelial permeability than platelets stored at room temperature [101,102].

Fresh and cold-stored whole blood is a growing alternative to the 1:1:1 ratio of pRBCs, plasma, and platelets. The use of whole blood can not only restore oxygen-carrying capacity, but also mitigate endotheliopathy and coagulopathy simultaneously and simplify the logistics of massive transfusion protocols. The use of whole blood has been limited to military medicine, but its use has been increasing recently in civilian trauma including several prehospital ground and air ambulance systems [103–106]. Although no large randomized control trial currently exists, the use of whole blood has been reported as feasible and associated with improved survival in several studies [107–111].

Transfusion of cryoprecipitate, a rich source of fibrinogen, factor VIII, and von Willebrand factor, and fibrinogen concentrate can be used for supplementing fibrinogen and enhancing hemo-
stasis. A minimal level of fibrinogen is required to maintain effective hemostasis. It has been reported that the use of fibrinogen concentrates or cryoprecipitate in trauma patients resulted in better survival [112–117]. However, there are controversies surrounding the effect of fibrinogen supplements on traumatic hemorrhage. A meta-analysis that included four randomized controlled trials [118] found that fibrinogen concentrate had no significant benefit on mortality, although the quality of evidence was graded low to moderate.

Current practice standards for DCR recommend early administration of tranexamic acid (TXA) for facilitating hemostasis. The CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significantly Haemorrhage 2) trial [119] demonstrated that administration of TXA within 3 hours of injury significantly reduced mortality, especially in hypotensive patients. Although a recent study [120] comparing TXA and placebo within 2 hours of injury in pre-hospital patients with hypotension (systolic blood pressure, < 90 mmHg) and tachycardia (heart rate, > 110 beats/min) did not result in significantly lower mortality, a subgroup analysis of patients with severe shock (systolic blood pressure, < 70 mmHg) or TXA administered within 1 hour of injury showed a survival benefit. Thus, TXA may be beneficial only in patients with severe shock and should be used shortly after the trauma event. The potential risk of TXA treatment is the development of venous thromboembolism (VTE), as demonstrated in retrospective studies of trauma patients [121,122]. Administration of TXA may increase the incidence of fibrinolysis shutdown, and patients in the CRASH-2 trial who received TXA at 3 hours after injury had an increased risk of death [66,123]. In addition, a small, single-center, randomized trial [124] compared placebo with 2 or 4 g TXA administration within 2 hours of trauma in patients requiring a transfusion of at least 1 unit of RBC and showed a dose-dependent increase of thromboembolic events. Furthermore, a large study administering TXA continuously for 24 hours in patients with acute gastrointestinal bleeding [125] showed a higher incidence of VTE. Thus, the use of TXA should be guided by coagulation status in patients. Conventional coagulation tests, such as prothrombin time, activated partial thromboplastin time, fibrinogen level, and platelet count, are unable to identify the status of hyperfibrinolysis or hypo-fibrinolysis. However, viscoelastic hemostatic assays can provide more comprehensive information about the coagulation status of patients rapidly and in real-time [22,126].

Permissive hypotension before and during definite bleeding control is advocated to limit ongoing hemorrhage by reducing hydrostatic pressure while maintaining a level of critical vital organ perfusion [127–132]. During permissive hypotension, providers control resuscitation so that systolic blood pressure does not exceed a targeted pressure (e.g., 100–110 mmHg). This strategy may reduce the degree of noncompressible torso hemorrhage until definitive surgical hemostasis can be achieved. However, prolonged definite bleeding control can produce permissive hypotension to result in additional accumulation of oxygen debt and must be balanced. Such strategies are even more complicated in patients in shock who also have traumatic brain injuries, in whom the recommended minimal systolic blood pressure is 110 to 120 mmHg [133,134]. The balance between permissive hypotension and avoiding the accumulation of additional oxygen debt is not trivial. The use of blood product resuscitation will help maximize the potential benefit of permissive hypotension.

CONCLUSION

Blood and the vascular endothelium can be considered a single organ system that can fail because of oxygen debt incurred during traumatic hemorrhage and its repair. The severity of this failure is exhibited through the development of EoT and ATC. This interplay among oxygen debt, EoT, and ATC drives the concept of "blood failure," where the disruption of normal physiological hemostasis results in a cascade of negative effects.

Efforts in managing blood failure involve a multifaceted approach. DCR strategies, such as permissive hypotension, early control of hemorrhage, and balanced transfusion of blood products, aim to limit the accumulation of oxygen debt and maximize its repayment, alleviate endothelial damage, and restore coagulation. Transfusion of pRBCs, plasma, and platelets and the use of TXA are essential components of DCR, contributing to hemostasis and mitigating the effects of ATC. Additionally, the use of whole blood, whether fresh or cold-stored, is emerging as a promising approach to address the holistic needs of trauma patients. The intricate relationships between these factors highlight the urgent need for comprehensive, integrated strategies that consider the interconnected nature of traumatic hemorrhage, blood failure, and its associated complications. This review sheds light on synergistic relationships and emphasizes the importance of multidisciplinary approaches to effectively manage traumatic hemorrhage and to mitigate its detrimental consequences.

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REFERENCES

22. Johansson PI, Stensballe J, Ostrowski SR. Shock induced endotheliopathy (SHINE) in acute critical illness: a unifying


49. Darlington DN, Craig T, Gonzales MD, Schwacha MG, Cap AP, Dubick MA. Acute coagulopathy of trauma in the rat. Shock


125. HALT-IT Trial Collaborators. Effects of a high-dose 24-h infusion of tranexamic acid on death and thromboembolic


INTRODUCTION

Rapid airway management is a critical component of care in the acutely ill and decompensating patient. National data suggest that there are nearly 400,000 intubations performed in the emergency department (ED) each year [1]. These intubations are at increased risk of complications due to their emergent nature [2]. One large multicenter trial of intubations among the critically ill [3] reported severe complications (i.e., hypoxia, hypotension, or cardiac arrest) in 18% of patients. Another ED-based study [4] reported a 12% adverse event rate, including events such as esophageal or mainstem intubation, hypoxia, and cardiac arrest. These event rates are likely even higher among patients with difficult airways or those in cardiac arrest [2].

Keywords: Intubation; Airway management; Ultrasound; Ultrasonography
The use of point-of-care ultrasound (POCUS) for emergency procedures to supplement or transform conventional techniques is increasing rapidly [5–9]. Therefore, it is not surprising that this has also extended to airway management [10,11]. Ultrasound can be used to assess for a difficult airway prior to intubation, allowing time for appropriate preparation and secondary plans for airway management. Additionally, POCUS can be used to confirm proper placement and depth of the tube. After intubation, ultrasound can be utilized to assess and identify problems preventing adequate ventilation. In the event of a known difficult intubation, POCUS can be leveraged to accurately identify the cricothyroid membrane even when external anatomy is challenging for palpation.

In this article, we will outline the application of ultrasound for airway assessment, confirmation, and management as well as provide guidelines for troubleshooting a decompensating ventilated patient.

**ASSESSMENT OF THE DIFFICULT AIRWAY**

Up to 90% of difficult airways are unanticipated [12]. The management of the difficult airway presents a significant challenge in clinical practice, and as such, various tools and techniques have been developed to help make accurate assessments prior to intubation. Traditionally, this has been done using risk factors and physical examination maneuvers. Numerous assessment tools have been reported with variable diagnostic accuracy [13]. The upper lip bite test is often considered to have the best diagnostic accuracy, though one study found that the sensitivity was only 67% [14–16]. Another commonly used tool, the modified Mallampati classification, had a sensitivity of 53% and a specificity of 89% [16].

Having the ability to assess the airway prior to intubation is a valuable skill and one that should be done quickly and accurately. POCUS is a helpful adjunct in airway assessments and can be done rapidly and noninvasively. There are several key measurements that can be used to predict difficult airways.

The first is the distance from the skin to the epiglottis (DSE) [17–22]. This measurement is taken at the level of the thyrohyoid membrane. The linear transducer is placed transversely in the midline just superior to the thyroid cartilage. The epiglottis is seen just deep to the thyrohyoid membrane and preepiglottic space and will appear as a hypoechoic linear structure above the air–mucosa interface (Fig. 1). The distance is then taken from the superficial skin edge to the anterior edge of the epiglottis. In a recent systematic review and meta-analysis [22], a DSE of ≥ 2.54 cm had a sensitivity of 82% and a specificity of 91% for predicting a difficult airway.

The second measurement is the distance from the skin to vocal cord (DSVC). This measurement is obtained by placing the linear transducer transversely in the midline over the thyroid cartilage. The strap muscles are seen anteriorly to the thyroid cartilage and the vocal cords are visualized just deep to the thyroid cartilage. The measurement is taken from the skin to the anterior commissure where the vocal cords join together (Fig. 2). A recent systematic review and meta-analysis [22] found that the DSVC had an overall sensitivity of 75% and a specificity of 72%. However, the literature is controversial with variable thresholds used and some even reporting an inverse association [23,24]. Therefore, the utility of this measure remains limited.

The third measurement is the hyomental distance (HMD), which is measured between the mentum of the mandible and the hyoid bone [21]. This measurement is obtained by placing the curvilinear transducer sagittally in the midline with the superior portion abutting the mandible. The mentum is seen as a hyperechoic structure with shadowing behind it on the superior portion of the image. The hyoid is a hyperechoic structure with shadowing behind it in the inferior portion. The measurement is taken between these two structures (Fig. 3). This distance has been reported as a single HMD, as a ratio of the HMD measured with the head in a ramped position compared to the head in neutral position (HMDR1), and the ratio of the HMD measured with the head...
Point-of-care ultrasound for airway management in maximal extension compared to the head in neutral position (HMDR2) [21]. Patients with a shorter HMD in neutral position (< 4.0 cm) were more likely to have a difficult airway [25]. Using a cutoff of 5.29 cm, HMD in the neutral position was 96.7% sensitive and 71.6% specific [26]. HMDR1 has less diagnostic utility with a 75% sensitivity and 76.2% specificity when using a threshold of 1.12 [27]. In contrast, HMDR2 has been reported to be 100% sensitive and 90.5% specific when using a threshold of 1.23 [27].

The fourth measurement is the tongue thickness. The tongue is measured in the midline at the widest diameter in a superficial to deep direction beginning at the skin (Fig. 4). Tongue thickness has been demonstrated to be greater in difficult versus easy laryngoscopy (6.1–6.2 cm vs. 5.3–5.8 cm) [28,29]. When using a threshold of 6.1 cm, tongue thickness is 71% to 75% sensitive and 72% specific [28,29].

Lin et al. [21] proposed a protocol for this assessment, the Difficult Airway Evaluation with Sonography (DARES). The DARES protocol uses DSE, tongue thickness, HMD, HMDR1, and HMDR2 to predict a difficult airway (Fig. 5). An airway is considered difficult if any of the findings are positive. While informed by existing literature, this algorithm has not been externally validated.

INTUBATION CONFIRMATION

After the intubation is performed, it is critical to confirm that the endotracheal tube (ETT) was correctly placed in the trachea. Data suggest that the first-pass success rate for endotracheal intubation is 84% in the ED and 78% in the prehospital environment [30,31]. Confirmation of ETT location typically involves direct visualization of the ETT passing through the vocal cords followed by one or more confirmatory techniques. Auscultation of bilateral breath sounds, visualizing misting of the ETT, or using an esophageal detector device have limited diagnostic accuracy for confirming ETT placement [11,32–37].

While waveform capnography is more accurate than the aforementioned approaches, it can be limited by false positives in the case of hypopharyngeal placement or recent ingestion of a carbonated beverage, as well as false negatives when expired CO₂ levels are low (e.g., flash pulmonary edema, massive pulmonary embolism, or cardiac arrest) [11,20,38,39]. Importantly, data suggest that the accuracy of end-tidal capnography in cardiac arrest may be as low as 64% [33–35]. Capnography also requires several positive pressure ventilatory attempts, which can increase gastric distension and increase the risk for aspiration.

In contrast, POCUS can allow rapid confirmation during or after the intubation attempt with a relatively short training period [10,40]. Among adults, POCUS is 99% sensitive and 97% specific [10,41]; whereas, POCUS is 92% to 100% sensitive and 100% specific in pediatric patients [42]. Studies have reported consistent accuracy regardless of the ETT size or type of transducer (e.g., linear, curvilinear) used [43,44].

To confirm the ETT location, begin by placing the ultrasound transducer across the trachea in a transverse orientation. The ideal location is just superior to the suprasternal notch, as this has
been shown to have superior visualization and diagnostic accuracy compared with other locations [45,46]. Confirmation can be performed in real-time (i.e., dynamic) or after the intubation (i.e., static). With the dynamic technique, the sonographer is assessing for rapid flutter-like movement as the ETT passes through the vocal cords (often referred to as the “snowstorm sign”) [20]. The static technique assesses for the appearance of either a thin hyperechoic membrane just posterior to the trachea (i.e., tracheal intubation) (Fig. 6) or a second air–mucosa interface referred to as the “double tract” sign (i.e., esophageal intubation) (Fig. 7) [20].

The literature has not demonstrated a significant difference in the accuracy between the static and dynamic techniques, so e-
ther are acceptable [10,47]. However, the static technique offers several unique benefits, including only requiring a single clinician (i.e., the intubator can also perform the POCUS immediately after the intubation is performed) and not placing the transducer on the neck during the intubation, which could make the intubation more challenging [20]. The major disadvantage is that it can be more difficult to locate the ETT behind the trachea due to the air artifact. In fact, data have shown reduced confidence and longer time to identification when the ETT is endotracheal versus esophageal [48]. To address this, some authors recommend twisting the ETT between one’s fingers to induce a false motion artifact [49,50]. While there was no significant difference in overall accuracy, ETT twisting has been shown to improve confidence and time to ETT identification [49]. Others have proposed infusing the ETT cuff with saline instead of air to better visualize the cuff [51–53].

In addition to direct visualization with transtracheal ultrasound, indirect signs such as lung sliding or diaphragmatic excursion can also be used to confirm ETT location. Bilateral lung sliding has been reported to be 92% to 100% sensitive and 56% to 100% specific [54–59]. Similarly, diaphragmatic motion has 91% to 100% sensitivity and 50% to 100% specificity [60–62]. When combined with transtracheal ultrasound, several studies [56,57] have found that the addition of lung sliding improves the accuracy compared with transtracheal ultrasound in isolation.

**ASSESSMENT OF ETT DEPTH AND UNILATERAL LUNG INTUBATION**

After confirming that the ETT is within the trachea, the next step is to assess the depth. If the ETT is placed too shallow, it can cause damage to the vocal cords or become dislodged [63–65]. If the ETT is placed too deep it risks barotrauma in the ventilated lung along with atelectasis and hypoxia in the unventilated lung [65,66]. Data suggest that incorrect ETT depth can occur in up to 15% of adults and 18% of children [67,68].

Clinical markers like chest rise and breath sounds have limited accuracy for mainstem intubation and cannot provide any insight into the ETT depth [69–71]. While chest radiography is considered the gold standard for ETT depth, it can take a significant amount of time, exposes the patient to radiation, and may delay other aspects of care in a critically ill patient [72].

In contrast, POCUS can provide rapid assessment of ETT positioning and assess for signs of mainstem intubation. In adults, transtracheal ultrasound had 84.8% accuracy for determining ETT depth and took on average 19 seconds to perform [73]. A recent systematic review and meta-analysis [74] found that ultrasound had 86.7% accuracy for detecting mainstem intubations, with a sensitivity of 93.0% and a specificity of 75.0%. In pediatric patients, one study [75] used a three-point technique (transtracheal ultrasound plus bilateral lung sliding) and reported 85.7% sensitivity and 98.3% specificity for mainstem intubation. Another study [76] used a saline-filled ETT cuff and was able to correctly identify ETT depth in 95% of cases.

To assess the depth of the ETT, start by placing the ultrasound transducer just superior to the suprasternal notch in the sagittal plane. Identify the thyroid cartilage, cricoid cartilage, and tracheal rings as hyperechoic, rounded structures in the near field with gray shadows. The ETT cuff will appear as a second, hyperechoic line directly posterior to these structures (Fig. 8). Saline can be instilled to improve visualization of the ETT cuff. If the cephalad border of the ETT cuff is seen at or above the first tracheal ring it is considered too high; between the second and eighth tracheal rings is considered adequate; and below the eighth ring or not visualized is considered too deep [73]. One additional benefit of POCUS is real-time assessment. If the ETT is visualized either above or below the ideal location, it can be advanced or retracted using real-time guidance.

If there is any concern for mainstem intubation or the ETT cuff cannot be adequately visualized, the transducer should be placed longitudinally on the anterior chest at the midclavicular line to assess for lung sliding bilaterally [54–59,75]. Unilateral lung sliding may suggest a mainstem intubation but can also be seen in pneumothorax or when large blebs are present [20]. To distinguish a mainstem intubation from other causes, one can assess...
for the presence of a lung pulse [65,77,78]. Lung pulse refers to the visualization of the rhythmic movement of the visceral pleura against the parietal pleura resulting from cardiac pulsations through an airless and motionless left lung. Lung pulse is 93% sensitive and 100% specific for right mainstem intubation [77].

IDENTIFYING THE CRICOTHYROID MEMBRANE

Cricothyrotomy is a critical procedure in scenarios where intubation and ventilation are unsuccessful. While uncommon, this is a high-risk procedure with increased risk of poor outcomes [79–81]. This procedure is fraught with complications stemming from anatomic challenges, high-stress conditions, and limited opportunities to practice the technique in a controlled, high-fidelity setting [82–84]. One study [85] found that only 36% of anesthesiologists were able to successful perform a cricothyrotomy in practice using landmark technique. Another study [86] found that among nonobese women, anesthesiologists could accurately identify the cricothyroid membrane (CTM) in 71% of cases, whereas that declined to 39% among obese patients.

Ultrasound can allow for direct visualization of the CTM, as well as any complicated anatomy, such as masses, enlarged thyroid glands, or vascular structures which would complicate an open cricothyrotomy. Ultrasound substantially improves the accuracy of CTM identification, with one study [87] reporting a twofold increase in successful identification in average patients. Among those with difficult or poorly defined anatomy, the accuracy improves by fivefold to tenfold [88,89].

Studies suggest the technique is both feasible and has a quick learning curve. Clinicians have shown to be able to identify the CTM membrane confidently and competently in both simulated and live patients [83,90,91]. Among clinicians without prior airway ultrasound experience, this has been shown to remain accurate with minimal training and has a high retention rate [84,92,93]. Moreover, this can be performed in less than 30 seconds across multiple patient populations, including pediatric and obese patients, and takes a comparable amount of time compared to the landmark-based approach [83,94,95].

The technique to identify the CTM is similar to ETT depth determination described above. Lay the patient supine with their neck extended. Start with the transducer in the sagittal plane on the anterior neck just inferior to the thyroid cartilage. Identify the tracheal rings, which will appear as a “string of pearls” leading from caudal to cranial direction. Immediately superior to that will be a larger ring (i.e., cricoid cartilage), followed by a hyperechoic membrane and then a larger rectangular structure (i.e., thyroid cartilage). The hyperechoic line between and just deep to the cricoid and thyroid cartilages is the CTM (Fig. 9). Slide a blunt needle under the cranial portion of the transducer down to the corresponding location of the CTM and subsequently mark the skin with a surgical pen [84].

Best practice is to mark the CTM prior to the intubation, rather than attempting to identify it after a failed intubation attempt. The CTM should be marked in the position that the cricothyrotomy would be performed. One study [96] found that the midpoint of the CTM moved caudally an average of 4.2 mm when changing the head of bed elevation from 90° to 0° and this effect was increased if the patient was obese or over age 70 years. Moreover, when the CTM is marked in the neutral neck position, the marking can move outside the CTM border when the neck is converted to full extension [97,98]. Fortunately, the CTM will return to the correct location when the patient is returned to the same position as when they were originally marked [99]. Therefore, it is advisable to mark the CTM in neck extension as close to the anticipated procedural position as possible prior to any attempted airway intervention [84,100].

ULTRASOUND FOR THE CRASHING VENTILATED PATIENT

Ultrasound also offers benefits in the assessment of the ventilated patient who experiences clinical deterioration. Traditionally, assessment of the postintubation patient has relied primarily on indirect assessment using structured algorithms, such as DOPES (dislodgement, obstruction, pneumothorax, equipment malfunc-
tion, stacking of breaths). However, as POCUS has expanded, we propose an update algorithm: Sono-DOPES. This algorithm builds upon previous work in DOPES (which had relied upon primarily physical examination findings) and adds ultrasound to enhance each stage (Table 1).

### CONCLUSION

Airway management is a common procedure within emergency and critical care medicine. Traditional techniques for predicting and managing a difficult airway each have important limitations. As the field has evolved, POCUS has been increasingly utilized for this application. Ultrasound can be utilized to predict difficult airways, confirm ETT location and depth, locate the CTM, and facilitate the assessment and management of the crashing patient on mechanical ventilation.

### ARTICLE INFORMATION

**Author contributions**

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

**Conflicts of interest**

The authors have no conflicts of interest to declare.

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**Data availability**

Data sharing is not applicable as no new data were created or analyzed in this study.

### REFERENCES

10. Gottlieb M, Holladay D, Peksa GD. Ultrasonography for the confirmation of endotracheal tube intubation: a systematic

### Table 1. Sono-DOPES for the crashing ventilated patient

<table>
<thead>
<tr>
<th>Potential etiology</th>
<th>Diagnostic assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dislodgment</td>
<td>Transtracheal ultrasound to assess for endotracheal vs. esophageal location and ETT depth</td>
</tr>
<tr>
<td>Obstruction of ETT</td>
<td>Lung ultrasound to assess for lung sliding to demonstrate air is entering the lungs through the ETT</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>Lung ultrasound to assess for bilateral lung sliding</td>
</tr>
<tr>
<td>Equipment malfunction</td>
<td>Lung ultrasound to assess for lung sliding</td>
</tr>
<tr>
<td>Stacking of breaths</td>
<td>Lung ultrasound to assess for bilateral lung sliding</td>
</tr>
<tr>
<td></td>
<td>Diaphragm ultrasound to assess for diaphragmatic expansion to suggest adequate air movement</td>
</tr>
</tbody>
</table>

DOPES, dislodgement, obstruction, pneumothorax, equipment malfunction, stacking of breaths; ETT, endotracheal tube.
35. Takeda T, Tanigawa K, Tanaka H, Hayashi Y, Goto E, Tanaka K.


52. Tessaro MO, Arroyo AC, Haines LE, Dickman E. Inflating the endotracheal tube cuff with saline to confirm correct depth using bedside ultrasonography. CJEM 2015;17:94–8.


61. Kerrey BT, Geis GL, Quinn AM, Hornung RW, Ruddy RM. A


88. Siddiqui N, Yu E, Boulis S, You-Ten KE. Ultrasound is superior to palpation in identifying the cricothyroid membrane in subjects with poorly defined neck landmarks: a randomized clinical trial. Anesthesiology 2018;129:1132–9.
Overview of clinical study designs

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The goal of a clinical study is to determine the factors associated with a disease and to assess the efficacy and safety of an investigational drug, procedure, or device. Since clinical study designs vary due to unique requirements of individual studies, the aims of this report are to educate researchers on the different types of studies and to assist researchers in choosing the optimal study type to fulfill their individual requirements. Clinical studies are classified into the two main types, observational studies and clinical trials, depending on the presence or absence of an intervention. Observational studies include case-control studies, cohort studies, and cross-sectional studies. Case-control and cohort studies may be prospective or retrospective, and case-control studies may be nested or not. Clinical trials may be pragmatic and may be controlled or noncontrolled; randomized or nonrandomized; open label or blinded; and parallel, crossover, or factorial. These observational and clinical trial designs are reviewed. Each type of clinical study has advantages and disadvantages. Therefore, researchers must consider these in choosing the design best suited for achieving their study objectives.

Keywords Clinical study; Observational study; Clinical trial; Study design; Bias

INTRODUCTION

Clinical studies are medical studies of groups of individuals. The goals of clinical studies are to determine associated disease factors and to assess the efficacy and safety of an investigational drug, procedure, or device for preventing, diagnosing, and treating disease. Clinical studies may test for the long-term effects or cost-effectiveness of an investigational treatment. There are two main types of clinical study, observational studies and clinical trials. In observational studies, investigators gather information on broad characteristics. For example, investigators may collect data through medical exams or questionnaires on the effects of lifestyle on cognitive health. Observational studies provide valuable information and may assist in identifying topics for clinical trials. Clinical trials test the safety and efficacy of medical, surgical, or behavioral interven-

What is already known
Multiple study designs exist to help determine the factors associated with a disease and to assess the efficacy and safety of an intervention.

What is new in the current study
In this paper we review multiple study designs and discuss their advantages and disadvantages.
Clinical study designs

Clinical study results have clinical, public, and economic impacts and need to be well-planned to provide valid study results.

Since study designs vary due to unique individual requirements, choosing the optimal study design is important. The aims of this article are to educate researchers on the different study designs and to assist those researchers in choosing optimal designs for fulfilling their research needs.

OBSERVATIONAL STUDY DESIGNS

Observational studies are those in which groups of individuals are monitored or outcomes are measured without manipulation or intervention to affect the result. Observational studies include case-control, cohort, and cross-sectional studies. Advantages and disadvantages of each type of observational study are listed in Table 1.

Case-control study
Case-control studies compare groups, such as subjects with a disease or condition under study (cases) to subjects without the disease or condition (controls). Investigators study the medical or lifestyle histories of those in each group to determine factors that may be associated with the disease or condition (Fig. 1). If a factor is found more commonly in the cases than in the controls, the investigator may hypothesize that the exposure is linked to the disease. For example, in the investigation of risk factors for depression in intensive care unit (ICU) patients, the patients with depression were defined as cases; and sex, age, length of ICU stay, and individual medications were considered as risk factors associated with depression [1].

Advantages and disadvantages
The main advantages of a case-control study are low cost and low time consumption. The case-control approach allows for study of rare diseases that require lengthy study periods. The case-control study design allows assessment of multiple factors at once.

A disadvantage is that bias is inherent in case-control studies. Case-control studies have the potential for recall bias, the increased likelihood that those with the outcome will recall and report exposures more frequently than those without the outcome. Recall bias may lead to conclusion of false associations between exposure and disease.

One of the aspects that is often overlooked is the selection of cases and controls. Appropriate selection of cases and controls to obtain a meaningful and scientifically sound conclusion is important and can be achieved by matching. Matching assists in risk factor or etiological identification that cannot be explained by other differences between the groups. Thus, choosing a control group that bolsters the strength of the case-control study and enhances the researcher’s ability to find valid potential correlations between exposures and disease states is important.

In addition to bias, the investigator must recognize the potential for confounding factors that result when a variable that is not being accounted for is related to both the exposure and the outcome. The potential for confounding is another disadvantage of case-control studies.

Cohort study
Cohort studies are a type of longitudinal study, an approach that follows study participants over time. Specifically, cohort studies recruit and follow study participants who share common characteristics. Baseline information on the individual cohort members are

<table>
<thead>
<tr>
<th>Study type</th>
<th>Advantage</th>
<th>Disadvantage</th>
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<tbody>
<tr>
<td>Case-control study</td>
<td>Less expensive, less time-consuming</td>
<td>Vulnerable to bias (recall bias, selection bias, confounding bias)</td>
</tr>
<tr>
<td>Cohort study</td>
<td>Effective to establish cause and effect</td>
<td>Possibility of selection bias, information bias</td>
</tr>
<tr>
<td>Nested case-control study</td>
<td>Can reduce the cost to perform the study</td>
<td>Require the selection of a new set of controls for each distinct disease</td>
</tr>
<tr>
<td>Case-cohort study</td>
<td>The ability to study several diseases using the same subcohort</td>
<td>Require a more complicated statistical analysis</td>
</tr>
<tr>
<td>Cross-sectional study</td>
<td>Useful to assess the prevalence of disease</td>
<td>Cannot infer causality</td>
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<td></td>
<td>Can suggest a natural progression with less cost</td>
<td>Cannot estimate incidence rate</td>
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<tr>
<td></td>
<td></td>
<td>Not good for studying rare disease</td>
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<td></td>
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<td>Susceptible to nonresponse bias and recall bias</td>
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of study. For example, to determine the effects of three aspects of care provided by primary physicians (physician specialty, continuity of care, and comprehensiveness of care) on patient use of the ED, investigators created a retrospective cohort of adults aged 18 years and older using provincial administrative databases that covered a 3-year span. The primary care variable and covariables were measured during an initial baseline period (the first 2 years of the study); visits to the ED for the primary outcome were measured during the last year of the study [3].

**Fig. 1.** Case-control study, prospective cohort study, and retrospective cohort study.

advantages and disadvantages

One of the advantages of cohort studies is their effectiveness in establishing cause and effect. Cohorts are usually large, allowing investigators to draw relatively confident conclusions regarding the links between risk factors and disease. In many cases, because participants are often free of disease at the commencement of the study, cohort studies are particularly useful at identifying the timelines over which behaviors contribute to disease development. Another advantage is that investigators can collect a wide variety of data in cohort studies that can be used in multiple ways. A study on the impact of smoking, for example, might reveal links with multiple types of diseases. Investigators can also compare degrees of risk among risk factors.

Like case-control studies, cohort studies are subject to bias. Some of the biases observed with cohort studies include selection bias and information bias. Selection bias results when exposure is linked to study participation. Individuals with an exposure may refuse to participate in the study at a higher rate than those without the exposure. Selection bias also occurs when the ex-
posed are lost to follow-up. Because of selection bias, interpretation of associations between exposures and outcomes is difficult. Information bias occurs when the data in past records are inaccurate in the evaluation of exposure status creating interpretation difficulties. Causal inference problems also result in prospective cohort studies when participants who are aware of their participation in a cohort alter their behavior during follow-up. In addition to bias, disadvantages of prospective cohort studies include their time consumption and expense compared to case-control studies. Retrospective cohort studies are more pragmatic; the use of historical data decreases time and expense requirements. However, retrospective approaches increase the risk of bias in sampling of the cohort due to missing data. Retrospective cohort studies are also weakened by the data fields available not being designed with the study in mind.

Case-control studies based within a defined cohort
This type of study combines some of the features of a cohort study with those of a case-control study design. When a defined cohort is embedded in a case-control study design, all baseline information is collected before the onset of disease, and the cohort is followed until onset of disease. One of the advantages of this design is the elimination of recall bias as the information regarding risk factors is collected before onset of disease. Case-control studies based within a defined cohort can be further classified into nested case-control studies and case-cohort studies.

Nested case-control study
This type of study design involves the selection of several controls for each case, typically from those still under observation at the time when the case developed the disease. A nested case-control study consists of a defined cohort with suspected risk factors and assignment of controls within the cohort to cases, subjects who develop the disease [4]. Over a period, cases and controls are identified and followed as per the study protocol. Hence, the case and control are matched in time and length of follow-up (Fig. 2A). When this study design is implemented, controls may become cases. The procedures for sampling in a nested case-control study follow. Select all those who become cases. Select controls randomly from those still at risk at time of case development (risk set), selection of five controls typically maximizes efficiency. Controls are time-matched to cases. Individuals can be controls more than once, and an individual selected as a control may later become a case. In the matching process, additional matching on confounders is often involved. One such study examined the association between incident injury after prescription opioid initiation and subsequent risk of opioid-related adverse events (ORAEs). The nested case-control study was conducted in a cohort of individuals 65 years and older. This assessment was of the association of prescription opioid use with recency of injury among older patients. ORAE cases were identified as patients who became inpatients or outpatients with a diagnosis code for opioid misuse, dependence, or poisoning. Using 1:4 matching, controls were randomly selected using incidence density sampling with matching criteria that included the year of cohort entry date and a disease risk score [5].

Nested case-control studies have some limitations. When more than one disease outcome is considered, a strict implementation of the nested case-control design requires selection of a new set of controls for each distinct disease outcome. Estimation of risk is not possible because the at-risk period is unknown. We can estimate rate, however, if the size and fraction of each risk set are known; but this is not a trivial matter, especially if there are time-dependent effects.

Fig. 2. Case-control study based within a defined cohort. (A) Nested case-control study. Controls are time-matched to the cases. (B) Case-cohort study. Subcohort is not time-matched to the cases.
Case-cohort study

Case-cohort study designs were proposed as an alternative to the nested case-control study design. This design requires only selection of a subcohort random sample and all cases. Cases are defined as those participants of the cohort who developed the disease of interest, but controls are identified before the cases develop (Fig. 2B). Controls are randomly chosen from all cohort participants regardless of disease of interest status, allowing for early collection of baseline data. Case-cohort studies are similar to nested case-control studies; the main difference between the two study types is the way in which controls are chosen. A case-cohort study was conducted to examine the association between the risk factors and hospitalization in a cohort of dog bite victims requiring ED visits. The risk factors included infection, complicated injury, host defense abnormality, number of previous evaluations for the injury, and anatomic location of the bite. The case-cohort design was chosen because cases could be identified in a well-defined administrative cohort, medical record review was required for each study patient, and the risk ratio was the effect measure of interest. Cases were cohort members who were admitted as inpatients directly from the ED. From the cohort, a simple random sample was selected for the subcohort comparison group. Some patients were included into both subcohort and case groups [6].

Compared to the nested case-control studies, a major advantage of the case-cohort design is the ability to study several disease outcomes using the same subcohort. For example, investigators interested in determining if smoking is a risk factor for both diabetes and lung cancer would require two control groups with a nested case-control design, while a case-cohort design only requires one subcohort. Unlike the nested case-control study, the case-cohort study can estimate rate or risk, since the measurement in the subcohort can be observed for any time up to variable event onset.

A case-cohort study has some limitations. Information bias can be increased when the subcohort is established after baseline. With much censoring, the subcohort becomes “thin” and may not be representative of the cohort. Also, statistical analysis is more complicated than with a nested case-control study.

Cross-sectional study

A cross-sectional study is a type of observational study that involves data collected at a defined time; a cross-sectional study analyzes data from a population, or a representative subset, at a specific point in time. These studies are often used to assess the prevalence of acute or chronic conditions but cannot be used to answer questions about the causes of disease or the results of interventions. That is, cross-sectional data cannot be used to infer causality because temporality is not known. Cross-sectional studies may involve special data collection, including questions about the past, but often rely on data originally collected for other purposes.

Advantages and disadvantages

The use of routinely collected data allows large cross-sectional studies to be conducted at little or no expense. A natural progression has been suggested from cross-sectional studies of routinely collected data that suggest hypotheses, to case-control studies that test these hypotheses more specifically, to more costly and time-consuming cohort studies and trials that provide stronger evidence.

Temporal association cannot be established as the information is collected at the same time point. If a study involves a questionnaire, the investigator can ask questions about onset of symptoms or risk factors in relation to onset of disease. The prevalence of a disease can be determined; the incidence cannot. Cross-sectional studies are not suited for studying rare diseases and are susceptible to biases such as nonresponse bias and recall bias.

CLINICAL TRIAL

A clinical trial is a prospective study of the effects of interventions or manipulations of interest. Since this type of study can provide the most convincing demonstration of evidence of causality, the design requires meticulous planning and resources to provide an accurate result.

General considerations

When designing a clinical trial, selecting a representative population that assures generalizability to the target population is of paramount importance, as is selection of appropriate endpoints. Endpoints need to be well-defined, reproducible, clinically relevant, and achievable. The types of endpoints are continuous, ordinal, nominal, and time-to-event; and the endpoint is typically classified as primary, secondary, or tertiary. An ideal endpoint is a purely clinical outcome; for example, cure or survival, and clinical trials can be long and expensive. Surrogate endpoints may be biologically related to the ideal endpoint and need to be reproducible, easily measured, related to the clinical outcome, affected by treatment, and occur earlier than the clinical outcome.
Controlled vs. noncontrolled trials
Clinical trials are divided into controlled versus noncontrolled clinical trials depending on the presence or absence of a control group for the investigational treatment of interest.

Uncontrolled trials
Uncontrolled trials are often used in the early phases of drug research, phases I and II, to determine pharmacokinetic properties or to investigate tolerated dose ranges. Uncontrolled trials can also be useful to study side effects, biochemical changes in long-term therapies, tolerance, interaction, or efficacy of drugs. Uncontrolled trials produce higher estimates of the mean effect than those obtained in a controlled trial since, by not having a control group acting as a reference, uncontrolled trials can induce erroneous impressions of the investigated drug [7]. Since these trials generate bias, the results of uncontrolled trials are considered less valid than those of controlled trials.

Controlled trials
The design of these trials includes at least one treatment group that is compared with a control group. The control group receives placebo or another active treatment. Both groups are studied simultaneously, except when the control group is derived from historical data or when some adaptive designs are used. Controlled trials are the most common in clinical phase III. Controlled trials allow the participant’s outcome to be discriminated from an outcome caused by other factors, such as the natural history of the disease or the expectations of the participant or the investigator.

Common controls are placebo control, active treatment control, control with dose comparison, and historical control. Particular care is required when attempting to use placebo control and historical control.

Placebo control
Placebo is defined as “an inert or innocuous substance used especially in a controlled experiment testing the efficacy of another substance (such as a drug)” [8]. This is especially useful if the outcome measured is subjective and should only be used if no permanent harm (death or irreversible morbidity) occurs by delaying available active treatment for the duration of the trial. The ethics of placebo-controlled studies is complex and continues to create a debate in the medical research community. According to the Declaration of Helsinki on the use of placebo released in October 2013, “the benefits, risks, burdens, and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances: where no proven intervention exists; the use of placebo, or no intervention, is acceptable; or where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the participants who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention. Extreme care must be taken to avoid abuse of this option” [9]. Hence, while designing a research study, both the scientific validity and ethical aspects of the study will need to be thoroughly evaluated.

Active treatment control
This design involves comparing a new drug with a standard drug or comparing the combination of new and standard therapies versus standard therapy alone. This design is more ethical than the placebo control, provided that approved drugs are available for the disease under study.

Control with dose comparison
Different doses or regimens of the same treatment are used as the active arm and control arm. The purpose is to establish a relationship between the dose and the efficacy and safety of the intervention. This design can include active and placebo groups in addition to the different dose groups. The design may be ineffective if the therapeutic range of the drug is not known.

Historical control (external and nonconcurrent)
In this design, the information from the controls is not obtained during the study but is from subjects who were treated at an earlier time or in a different setting. This design has an advantage when studying rare conditions in which difficulty arises in generating a sample size. This design is also cost-effective and time-saving. However, the design has many disadvantages. Randomization and blinding are not possible, and the comparability of the current intervention with the historical control is difficult due to the differences in baseline characteristics of the subjects. The comparability problem can be addressed to some extent by statistical methods, but the information obtained may not be accurate or reliable and may lack uniformity and/or completeness.

Randomized vs. nonrandomized clinical trials
Clinical trials are randomized or nonrandomized based on the method used to allocate a participant to a treatment or control group.
**Randomized clinical trials**
A randomized clinical trial involves randomizing participants with similar characteristics to one of two or multiple groups, the group(s) that receives the intervention/experimental therapy and the other group(s) that received the placebo or standard of care. Randomization is typically performed using a computer software package. Hence, we can measure the outcomes and efficacy of the intervention or experimental therapy being studied without bias as participants with similar baseline characteristics have been randomized to their respective groups. Randomized controlled trials are the gold standard for clinical study. However, this study design is generally not applicable to rare and serious disease processes due to the ethics involved in treating affected individuals with a placebo.

**Nonrandomized trials**
A nonrandomized trial involves an approach of selecting controls without randomization, usually allocation of participants into groups by the investigator. This may also result from selection of participants and controls based on day of the week presentation or assignment to a particular clinician. This type of participant and control selection becomes predictable. Therefore, there is bias introduced that can impact the validity of the results.

**Open-label vs. blind trials**
Clinical trials are divided into open-label versus blind trial based on participants’ or investigators’ awareness of the treatment group to which participants have been allocated.

**Open-label trials**
Certain treatments cannot be blinded such as surgeries or if the treatment group requires an assessment of the effect of intervention. In this case, open-label trials are planned in which both trial participants and investigators know the group assignment of the participants.

**Blind trials**
This is a method used in clinical trials to reduce the risk of intentional or unintentional bias. There are three forms of blinding: single, double, and triple blind. In a single-blind study, only the participants do not know their group assignment until the trial is over. In double-blind studies, both the study participants and the investigator are unaware of the group to which subjects were allocated. Double-blind studies are typically used in clinical trials to test the safety and efficacy of drugs. In triple-blind studies, participants, investigators, and data analysts are unaware of the group allocation. Those who are directly or indirectly involved in the trial, such as caregivers and data recorders, should also be blinded to the group allocation of the trial participant in order to increase the effect of blinding.

**Parallel, crossover, and factorial design trials**
Based on the treatment structure, clinical trial designs are classified into parallel, crossover, and factorial designs. A summary of the advantages and disadvantages of each design is provided in Table 2.

**Parallel design trials**
A parallel design of a clinical trial is a design in which two or more groups of participants receive different interventions. Participants are assigned to one of the treatment arms at the beginning of the trial and continue in that arm throughout the length of the trial (Fig. 3). This is the most common clinical trial design. Parallel design has two advantages over the crossover design described later. All other conditions being the same, the duration of the study is shorter and the visits required are fewer, which results in a study that is less burdensome for the participant. The statistical analysis requires fewer assumptions, which, if not verified, would reduce the reliability of the conclusions. The weakness of the parallel design is that it requires a larger sample size than the crossover design.

**Crossover design trial**
The crossover clinical trial is a design in which all participants receive the same two or more treatments, but the order of receipt depends on the group of assignment. Hence, in this type of design, there are two groups that undergo the same intervention/experiment at different time periods. That is, each group serves as a control while the other is undergoing the intervention/experiment. A “washout” period is recommended in order to eliminate

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**Table 2. Advantages and disadvantages of parallel, crossover, factorial design trials**

<table>
<thead>
<tr>
<th>Trial design</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parallel</td>
<td>Shorter duration of the study and less burdensome for the participant</td>
<td>Require a larger sample size comparing to crossover design</td>
</tr>
<tr>
<td></td>
<td>Require fewer assumption for the statistical analysis</td>
<td></td>
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<tr>
<td>Crossover</td>
<td>A smaller sample size comparing to parallel design</td>
<td>Possibility of carryover effect</td>
</tr>
<tr>
<td>Factorial</td>
<td>Efficiency from fewer participants than separately performed trials</td>
<td>Difficulty for experimenting with more than one factors, or many levels</td>
</tr>
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</table>
residual effects of the intervention or experiment (carryover effect) when the experiment group transitions to the control group, or vice versa (Fig. 3).

The main advantage of the crossover design is that each subject acts as a their own control. Therefore, a smaller number of subjects is required in comparison to parallel group studies because of removing of participant variation in this way. This type of trial can only be considered when the disease persists for a relatively long period. Hence, crossover trials are mostly used in studying chronic diseases. The main disadvantage is that the carryover effect may be aliased (confounded) with direct treatment effects as they cannot be estimated separately.

**Factorial trial**

In a factorial trial, two or more intervention comparisons are carried out simultaneously. For example, participants may be randomized to receive aspirin or placebo and randomized to receive a behavioral intervention or standard care. This factorial trial has two factors, each of which has two levels; there are called 2 x 2 factorial trials (Fig. 3). When designing a factorial trial, the main intention of investigators is to achieve "two trials for the price of one"; and the assumptions are that the effects of the different active interventions are independent, and that there is no interaction (no synergy or antagonism) between the treatments. The interaction effect between the two treatments can be tested by a proper methodology. Since a 2 x 2 factorial trial can be seen as two trials addressing different questions, it is important that both parts of the trial are reported as if they were part of a two-arm parallel group trial. Thus, in the example given, we would expect to view the results for aspirin versus placebo, including all participants regardless of whether they had behavioral intervention or standard care, and likewise of the behavioral intervention. An evaluation of the interaction between the two treatments based on the factorial design may also be available.

The factorial design allows investigators to obtain evidence about efficacy from fewer patients than would be needed if treatment A and B were individually tested in two separate trials. The main disadvantage is the difficulty of experimenting with more than one factor or level. A factorial design must be planned meticulously, as an error in one of the levels, or in the general operationalization, will jeopardize a vast amount of work.

**Pragmatic clinical trial design**

A classical clinical trial may not be adequately reflective of practice because the trial may have been optimized to determine intervention efficacy. Because such trials were also performed with a relatively small size of highly selected participants at sites with experienced investigators, the trials could overestimate benefits and underestimate harm of the intervention. These concerns create the need for more pragmatic trials designed to demonstrate the actual effectiveness of the intervention in more generalized settings. Trial design can be more pragmatic when considering four domains: the study population, the setting of the trial, operationalization of the intervention, and the outcome measures [10,11]. In order to provide the comprehensive evaluation of comparative clinical effects of 0.9% saline and balanced crystalloids across the full spectrum of diseases typical for hospitalized adults, a pragmatic trial was conducted among noncritically ill adults who were subsequently hospitalized outside an ICU. This trial was designed to consider broad eligibility criteria, large sample size, study procedures that included routine care, and execution of the trial by clinical personnel [12,13].
CONCLUSION

The different types of clinical studies are used for different reasons. Selecting the best design for a given study is critical to a successful outcome. In terms of the quality of evidence, a clinical trial is superior to an observational study. Observational studies are, however, conducted much more frequently than clinical trials. Ethical considerations and cost are main reasons that observational studies are frequently employed. A case-control study is a valuable tool for exploring risk factors for rare diseases or when other types of study are not feasible. Investigators explore possible associations between exposure and disease through case-control studies, and data from case-control studies can provide a focus for future studies. Then, through cohort studies or clinical trials, the evidence of an association between exposure and disease can be increased. Cohort studies are often complex, large, and long in duration. However, with careful planning and implementation, cohort studies are valuable in providing healthcare evidence. To reduce cost and achieve the same goal as a cohort study, nested case-control and case-cohort study are alternatives. These types of studies are based on large cohorts and can be useful in "big data" analysis [14]. Nested case-control and case-cohort study designs are efficient in terms of cost and can be used to evaluate the relationship between exposure and disease. Compared to a nested case-control design, the case-cohort design is more efficient and allows an investigator to study several disease outcomes using the same random sample [15]. While there are some advantages in observational studies, biases are inherent and should be addressed. Recently, as studies using "big data" have become possible, well-designed historical control studies have increased. In clinical trials, appropriate control group selection is vital. The clinical trial study should be planned so that those involved in the study, including participants, are blinded to the maximum extent possible. The classical trial designs are parallel, crossover, and factorial designs. In addition, although not applicable to all diseases or clinical trials, new methodologies such as adaptive designs can shorten the duration of a clinical trial. Investigators should also consider pragmatic clinical trials that are more efficient, patient-centered, and empirical and are conducted in order to provide more valuable clinical and policymaking information.

ARTICLE INFORMATION

Conflicts of interest
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REFERENCES

Clinical study designs

Protective role of kallistatin in oxygen-glucose deprivation and reoxygenation in human umbilical vein endothelial cells

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Objective Ischemia-reperfusion (IR) injury is implicated in various clinical diseases. Kallistatin attenuates oxidative stress, and its deficiency has been associated with poor neurological outcomes after cardiac arrest. The present study investigated the antioxidant mechanism through which kallistatin prevents IR injury.

Methods Human umbilical vein endothelial cells (HUVECs) were transfected with small interfering RNA (siRNA) targeting the human kallistatin gene (SERPINA4). Following SERPINA4 knockdown, the level of kallistatin expression was measured. To induce IR injury, HUVECs were exposed to 24 h of oxygen-glucose deprivation and reoxygenation (OGD/R). To evaluate the effect of SERPINA4 knockdown on OGD/R, cell viability and the concentration of kallistatin, endothelial nitric oxide synthase (eNOS) and total NO were measured.

Results SERPINA4 siRNA transfection suppressed the expression of kallistatin in HUVECs. Exposure to OGD/R reduced cell viability, and this effect was more pronounced in SERPINA4 knockdown cells compared with controls. SERPINA4 knockdown significantly reduced kallistatin concentration regardless of OGD/R, with a more pronounced effect observed without OGD/R. Furthermore, SERPINA4 knockdown significantly decreased eNOS concentrations induced by OGD/R (P<0.01) but did not significantly affect the change in total NO concentration (P=0.728).

Conclusion The knockdown of SERPINA4 resulted in increased vulnerability of HUVECs to OGD/R and significantly affected the change in eNOS level induced by OGD/R. These findings suggest that the protective effect of kallistatin against IR injury may contribute to its eNOS-promoting effect.

Keywords Heart arrest; Reperfusion injury; Reactive oxygen species; Nitric oxide; Nitric oxide synthase
INTRODUCTION

Ischemia-reperfusion (IR) injury refers to a series of clinical and experimental consequences triggered by tissue ischemia from insufficient oxygen supply, followed by subsequent reperfusion [1,2]. IR injury is implicated in various clinical diseases, including myocardial infarction, stroke, and limb ischemia [3–5]. The process of reperfusion following ischemia stimulates the formation of reactive oxygen species (ROS) and oxidative stress, resulting in various inflammatory responses, leading to local tissue injury and remote organ dysfunction [6,7].

Kallistatin is an endogenous serine proteinase inhibitor that binds to the kallikrein protein and inhibits kallikrein activity [8,9]. Kallistatin exhibits various functions such as antioxidation, anti-inflammation, and antiangiogenesis activities [10]. The antioxidative property of kallistatin is accomplished by attenuating ROS formation through inhibition of the oxidase activity of the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) [11]. Furthermore, kallistatin promotes the synthesis of endothelial nitric oxide synthase (eNOS), sirtuin 1, and forkhead box protein O1 enzymes, thereby reducing oxidative stress [11–14]. As a result of its antioxidative property, kallistatin has a protective effect against IR injury in murine myocardial and renal IR injury models [15,16]. In our previous study [17], the association between low-serum kallistatin level and poor neurological outcomes in out-of-hospital cardiac arrest patients was revealed through a proteomics approach. The study suggested that kallistatin deficiency could potentially diminish the endogenous antioxidative defense capacity of nerve cells, leading to increased neuronal damage and unfavorable neurological outcomes following cardiac arrest.

We hypothesized that kallistatin deficiency would enhance cell death caused by IR injury, possibly resulting from the attenuation of the eNOS-promoting effect of kallistatin. To validate this hypothesis, we conducted experiments using human umbilical vein endothelial cells (HUVECs) in which kallistatin expression was suppressed by ribonucleic acid interference. An in vitro model mimicking IR injury was created by applying oxygen-glucose deprivation and reoxygenation (OGD/R) to HUVECs. The primary objective of this study was to investigate the antioxidative mechanism of kallistatin in the prevention of IR injury.

METHODS

Cell culture

HUVECs (Cat. C2517AS, Lonza) were cultured in EGM-2 Endothelial Cell Growth Medium-2 BulletKit (Cat. CC3162; Lonza) containing 10% fetal bovine serum. The HUVECs were incubated for 24 hours at 37 °C in a humidified atmosphere with 95% air and 5% carbon dioxide. After reaching 90% confluence, the cells were seeded on 96-well plates (2 × 10^4 cells/well) or 6-well plates (2 × 10^6 cells/well) for subsequent experiments.

Small interfering ribonucleic acid transfection

To generate SERPINA4 knockdown cells, HUVECs were transfected with small interfering RNA (siRNA) targeting the human kallistatin gene SERPNA4. The ON-TARGETplus human SERPINA4 (5267) siRNA-SMARTpool (25 nM, target sequence: 5'-GGUGAGA-GAGUUCGAGUAACA-3', 5'-CAAUCUC-AUGCUGAACAGA-3', 5'-CCACCAGCUUCGCAUCAA-3', 5'-GCAAACUG-AGGGAGAUA-3'; Cat. L016371000050, Dharmacon) and siGLO RISC-Free Control siRNA (Cat. D0016000105, Dharmacon) as control were used for transfection. HUVECs were treated with these siRNAs using DharmaFect1 transfection reagent (Cat. T2001-03, Dharmacon) according to the manufacturer’s instructions for 6 hours and then cultured for 18 hours in complete media before further experiments.
Oxygen-glucose deprivation and reoxygenation
Transfected HUVECs were exposed to 90 minutes of OGD followed by 22.5 or 46.5 hours of reoxygenation. To induce OGD, complete medium was replaced with Dulbecco’s Modified Eagle Medium without glucose (Cat. 11966025, Thermo Fisher Scientific), and the cells were placed in a hypoxic chamber (Cat. INCO108, Memmert) with a gas mixture of 95% nitrogen and 5% carbon dioxide. After 90 minutes of OGD, the medium was changed back to the complete medium, and the cells were returned to the chamber with 95% air and 5% carbon dioxide for 22.5 or 46.5 hours of reoxygenation.

Cell viability assay
To determine the optimal duration of OGD/R with significant effects on cell survival, cell viability was assessed 22.5 or 46.5 hours after reoxygenation using Cell Counting Kit-8 (CCK-8; Dojindo Laboratories), which uses the tetrazole assay method with modified 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide. After 24 or 48 hours of OGD/R, CCK-8 solution (10 μL/well) was added and the cells were incubated for 2 hours at 37 °C. Subsequently, the absorbance at a wavelength of 450 nm was measured. We also assessed the cell viability of HUVECs treated with control or SERPINA4 siRNA and exposed to OGD/R using the methods described above to evaluate the effect of SERPINA4 knockdown on OGD/R.

Measurement of kallistatin, eNOS, and total NO concentration
To evaluate the effect of SERPINA4 knockdown on kallistatin expression and OGD/R, the kallistatin concentration in the culture medium was measured with the SERPINA4 Human ELISA Kit (Cat. KA3892, Abnova). To investigate the association between the eNOS-promoting property of kallistatin and its protective effect against IR injury, we measured the eNOS and total NO concentrations. The eNOS concentration in the culture medium was measured using the Human eNOS ELISA Kit (Cat. MBS8291345, MyBioSource), while the total NO concentration in the culture medium was measured using the Total Nitric Oxide and Nitrate/Nitrite Parameter Assay Kit (Cat. KGE001, R&D Systems).

Statistical analysis
To compare cell viability and concentrations of kallistatin, NO, and eNOS among experimental groups, we conducted one-way analysis of variance with Tukey post hoc test. Data were reported as mean±standard error. Statistical analysis was performed using IBM SPSS ver. 27.0 (IBM Corp). The level of statistical significance was set at P < 0.05.

RESULTS
Time-dependent effect of OGD/R on HUVECs
HUVECs exposed to 90 minutes of OGD followed by either 22.5 or 46.5 hours of reoxygenation exhibited reduced viability compared with control cells. The decrease in cell viability after OGD/R was significant at both 24 hours (P < 0.05) and 48 hours (P < 0.001), with a more pronounced effect at 48 hours (Fig. 1). As 24 hours of OGD/R was sufficient to induce a significant decrease in cell viability, we selected 24 hours of exposure for further experiments.

Effects of SERPINA4 siRNA transfection on kallistatin expression in HUVECs
The kallistatin concentration in the culture medium did not show any significant differences between the control cells without any treatment (21.1 ± 2.1 pg/mL) and the cells transfected with control siRNA (20.5 ± 3.3 pg/mL, P = 0.981). However, HUVECs transfected with SERPINA4 siRNA demonstrated a significantly lower kallistatin concentration in the culture medium (2.5 ± 0.7 pg/mL) compared with both the control cells (P < 0.001) and the cells transfected with control siRNA (P < 0.001) (Fig. 2). These results confirmed the successful SERPINA4 knockdown by SERPINA4 siRNA transfection.
Effects of SERPINA4 knockdown on cell viability and kallistatin expression in HUVECs exposed to OGD/R

In HUVECs transfected with either control siRNA or SERPINA4 siRNA, OGD/R significantly reduced cell viability (control siRNA, P < 0.01; SERPINA4 siRNA, P < 0.001) (Fig. 3). Cell viability in HUVECs exposed to OGD/R was significantly lower in the SERPINA4 knockdown cells compared with HUVECs transfected with control siRNA (P < 0.001).

We also measured the kallistatin concentration in the culture medium of the HUVECs with or without OGD/R. OGD/R significantly reduced the kallistatin concentration in the culture medium of the HUVECs transfected with control siRNA (P < 0.01). However, OGD/R did not induce a significant difference in the kallistatin concentration in the culture medium in HUVECs with SERPINA4 knockdown (P = 0.999). SERPINA4 knockdown led to a significant reduction in kallistatin concentration regardless of OGD/R, with a more pronounced effect observed without OGD/R (without OGD/R, P < 0.001; with OGD/R, P < 0.01) (Fig. 4).

Effects of SERPINA4 knockdown on eNOS expression and total NO concentration in HUVECs exposed to OGD/R

OGD/R did not induce a significant difference in the eNOS concentration in the culture medium of the cells transfected with either control siRNA (P = 0.362) or SERPINA4 siRNA (P = 0.527) (Fig. 5). Nevertheless, SERPINA4 knockdown resulted in a significant reduction in the eNOS concentration in the culture medium regardless of OGD/R (P < 0.01). OGD/R significantly reduced the total NO concentration in the culture medium of the HUVECs transfected with control siRNA (P < 0.05). In contrast, OGD/R did not induce a significant change in the total NO concentration in the culture medium of the SERPINA4 knockdown cells (P = 0.17). Additionally, the total NO concentration in the culture medium of HUVECs exposed to OGD/R was not significantly different between the HUVECs transfected...
with control siRNA and SERPINA4 knockdown cells (P = 0.728) (Fig. 6).

**DISCUSSION**

In the present study, we investigated the antioxidant mechanism of kallistatin in preventing IR injury. We found that exposure to OGD/R reduced HUVEC viability, and this effect was more pronounced in the SERPINA4 knockdown cells. SERPINA4 knockdown significantly decreased eNOS concentrations induced by OGD/R (P < 0.01) but did not significantly affect the change in total NO concentration (P = 0.728). These results confirm the protective role of kallistatin against IR injury, implying that its potential antioxidant mechanism might be attributed to its enhancement of eNOS expression.

Our study provides experimental evidence demonstrating that a deficiency of kallistatin led to reduced cell viability in response to IR injury. We used the OGD/R method to mimic IR injury. OGD/R is commonly used as an in vitro model for simulating ischemic stroke, and it has been widely accepted as a representative model that mirrors the conditions observed in in vivo models of brain ischemia [18,19]. Additionally, OGD-induced cardiac myocyte injury is commonly used as a model for myocardial IR injury during cardiovascular disease [20–22]. OGD/R is also used as an acute kidney injury model to replicate the effects of renal IR [23]. Given the extensive use of OGD/R in previous studies to investigate IR injury, including studies involving HUVECs [24–26], we selected this model to replicate IR injury in HUVECs for our study.

A previous study [12] demonstrated that kallistatin enhanced eNOS levels and NO production in a dose-dependent manner, which was mediated by kallistatin binding protein Kruppel-like factor 4. Although it was the first study that highlighted the eNOS-promoting effect of kallistatin, this study primarily aimed to investigate the anti-inflammatory effect of kallistatin rather than the antioxidant mechanism. Additionally, the study did not explore the impact of kallistatin administration on cell survival. Another study that investigated the protective role of kallistatin against oxidative stress–induced endothelial cell injury revealed that kallistatin suppressed tumor necrosis factor-α (TNF-α)-induced ROS formation and cellular apoptosis [13]. The effect was blocked by the knockdown of eNOS expression. Although Shen et al. [13] suggested that eNOS mediated the cell-protective effect of kallistatin against oxidative stress, it did not explore the direct protective effect of kallistatin against IR injury by kallistatin depletion or knockdown. Several studies have used kallistatin knockdown techniques [27–29]. One study [28] used kallistatin knockdown mice to investigate the role of kallistatin in endothelial senescence. The results confirmed that kallistatin knockdown exacerbated lung endothelial cell senescence and resulted in reduced levels of eNOS. However, the study did not use an IR injury model and primarily focused on senescence without specifically investigating cell viability. Our study is distinct with previous research in several ways. First, we used the OGD/R model to induce
IR injury in HUVECs, with the primary objective of investigating the antioxidant mechanism. Second, we used kallistatin knockdown cells and assessed cell viability to examine the direct cell-protective effect of kallistatin, not the effect of its mediator eNOS or NO. However, we also measured eNOS and NO expression to elucidate kallistatin’s antioxidative mechanism, particularly through its eNOS-promoting effect.

This study has several limitations. First, we were unable to directly confirm whether the suppression of kallistatin expression had a statistically significant effect on the alteration of NO expression in HUVECs exposed to OGD/R. Kallistatin promotes NO production by enhancing the expression of eNOS. NO, in turn, exhibits antioxidative and anti-inflammatory effects by inactivating various proteins such as vascular endothelial growth factor, TNF-α, transforming growth factor-β, nuclear factor-κB, and NADPH oxidase [11]. Therefore, it is crucial to confirm the direct link between kallistatin’s eNOS-promoting effect and increased NO production to explain its antioxidative property. However, this link was not confirmed in our study. Notably, although not statistically significant, the mean total NO concentration of HUVECs exposed to OGD/R was lower in SERPINA knockdown cells (22.3 μM) compared with HUVECs transfected with control siRNA (24.6 μM), suggesting that eNOS suppression from kallistatin knockdown might have impacted NO concentration. Thus, further investigation to fully elucidate the relationship between kallistatin, eNOS, and NO production in the context of IR injury is warranted.

Second, our study focused solely on investigating the protective effect of kallistatin against IR injury primarily attributed to its antioxidative property. Kallistatin possesses diverse biological activities, in addition to its antioxidative function, including anti-inflammatory and anticoagulant properties [10]. While oxidative stress is a critical factor contributing to tissue injury by IR processes, tissue hypoperfusion induced by local inflammation and coagulation also plays a significant role [30]. Considering the multifaceted nature of kallistatin functions, it is likely that its protective effect against IR injury arises from a combination of its antioxidative, anti-inflammatory, and anticoagulant properties. Thus, the precise mechanisms underlying kallistatin’s protective effects need further investigation, which will contribute to the comprehensive understanding of its various functions. Additionally, assessing also the morphological changes of the cells would contribute to a deeper understanding of the underlying mechanisms.

Third, this study focused on in vitro experiments. Consequently, we are unable to definitively conclude that kallistatin suppression induces susceptibility to IR injury in an in vivo environment. To overcome these limitations and to determine the protective effect of kallistatin on IR injury in vivo, animal experiments with the inhibition of kallistatin expression on nerve cells are warranted.

Fourth, this study was based on our previous research [17], which primarily focused its clinical attention on cardiac arrest patients. However, the in vitro model used in this study was not the model representing cardiac arrest. To date, knowledge regarding the mechanism of action of kallistatin in cardiac arrest patients is limited. Tissue ischemia caused by cardiac arrest induces hemodynamic and metabolic disturbances, leading to tissue injury [30–32]. Subsequent reperfusion through cardiopulmonary resuscitation (CPR) and the return of spontaneous circulation results in the generation of ROS, leading to further oxidative cell injury with compromised cell membrane and mitochondrial function [30–32]. Consequently, it can be inferred that cardiac arrest and subsequent CPR represent typical forms of IR injury, suggesting that kallistatin may play a role in this process. Therefore, to further investigate the role of kallistatin in the context of cardiac arrest, future research using cardiac arrest models in small animals or in vitro models using myocyte cells will be necessary.

Finally, an experiment to determine the effect of kallistatin administration on IR injury was not conducted. To become a therapeutic target for improving outcomes, a substance must be associated with a poor prognosis, and addition of the substance should improve the outcome [33,34]. However, in this study, the preparation of an adenovirus vector containing human kallistatin and the purification of recombinant kallistatin were too complicated, and it was difficult to determine the timing of kallistatin administration in the OGD/R model. Thus, experiments to confirm the effect of kallistatin administration were not conducted. To ascertain the potential therapeutic benefits of kallistatin, further studies investigating the effects of kallistatin supplementation on IR injury are warranted. In one study [15] that investigated the effect of kallistatin on cardiac function after myocardial IR injury, kallistatin gene delivery significantly reduced IR-induced cardiomyocyte apoptosis, promoted cardiac eNOS activation, and increased NO formation. However, the IR model used in the previous study [15] involved ligation of the left anterior descending coronary artery, which is not representative of cardiac arrest. Therefore, if cell or animal studies with a cardiac arrest model validate that kallistatin supplementation yields a protective effect against IR injury, it could provide valuable insights into the potential utilization of kallistatin as a therapeutic target.

In summary, transfection of HUVECs with SERPINA4 siRNA effectively suppressed kallistatin expression. Knockdown of SERPINA4 resulted in reduced cell viability in response to OGD/R and
significantly affected the change in eNOS level induced by OGD/R. These findings suggest that the protective role of kallistatin against IR injury might contribute to its property of enhancing eNOS expression. Further animal studies are needed to confirm the protective effect of kallistatin against IR injury in an in vivo environment.

ARTICLE INFORMATION

Author contributions
Conceptualization: WYK, SYS, GYS; Formal analysis: YWU, WYK; Investigation: YWU, WYK; Supervision: WYK, SYS, GYS; Writing–original draft: YWU; Writing–review & editing: all authors. All authors read and approved the final manuscript.

Conflicts of interest
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Data availability
Data analyzed in this study are available from the corresponding author upon reasonable request.

REFERENCES

18. Babu M, Singh N, Datta A. In vitro oxygen glucose depriva


A comparative study of intranasal desmopressin and intranasal ketamine for pain management in renal colic patients: a randomized double-blind clinical trial

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Objective Urolithiasis is one of the most common urological diseases worldwide, usually presenting as renal colic that leads to severe pain that requires analgesic treatment. This study aimed to compare the efficacy of ketamine and desmopressin in the pain management of renal colic patients.

Methods This double-blind, randomized clinical trial was conducted on renal colic patients referred to the emergency department from June 2021 to July 2022. Patients were randomly assigned to three groups. In the desmopressin group, patients were treated with intranasal desmopressin and intravenous ketorolac. The ketamine group was treated with intranasal ketamine and ketorolac. The control group received ketorolac and an intranasal placebo. Vital signs were evaluated at baseline and 60 minutes; and pain scores were assessed at baseline, 10, 30, and 60 minutes after treatment.

Results Enrollment included 135 patients, the mean (standard deviation) age was 44.1±11.4 years, and 82 (60.7%) were men. The mean visual analog scale scores were significantly lower at 10, 30, and 60 minutes in the ketamine group (5.6±1.2, 3.0±1.1, and 0.9±0.9, respectively) compared to the control (8.2±1.1, 5.1±2.0, and 2.3±2.6, respectively) and desmopressin (6.7±1.8, 4.2±2.2, and 1.3±1.4, respectively) groups (P<0.05). Although patients in the desmopressin group had lower mean pain scores than the control group at 10, 30, and 60 minutes, this difference was only significant at 10 minutes after the intervention (P<0.05). No significant differences in vital signs were found at 60 minutes after treatment.

Conclusion Ketamine showed more favorable analgesic effects in renal colic patients than desmopressin, although desmopressin showed efficacy in the first minutes posttreatment.

Keywords Emergency department; Ketamine; Desmopressin; Intranasal pain

INTRODUCTION

Urolithiasis is one of the most common urological diseases worldwide, with a 1% to 13% prevalence depending upon region [1,2]. Urolithiasis commonly presents to the emergency department (ED) as renal colic with extreme pain. Millions of patients worldwide present to the ED an-
Intranasal ketamine in renal colic

What is already known
This study aimed to compare the efficacy of ketamine and desmopressin in the pain management of renal colic patients. The therapeutic effect of desmopressin has been studied in the treatment of renal colic.

What is new in the current study
Ketamine showed more favorable analgesic effects in renal colic patients than desmopressin.

nually with renal colic. The rate of renal colic presentations at EDs has been reported to be 6.7 to 27.9 per 1,000 ED visits [3]. Renal colic is a severe pain in the flank or abdomen, generally radiating to the groin or genital area, caused by obstructions in the urinary tract. The leading cause of renal colic is urinary flow obstruction and increased pressure proximal to the obstacle [1–3]. Although this pain is intense, most urinary tract stones are eliminated spontaneously and do not require surgical intervention. Therefore, effective analgesic treatment is a primary goal in managing renal colic [4–6].

Many therapeutic agents are prescribed for pain management in patients with renal colic, including opioid and nonopioid drugs. The commonly used nonopioid drugs are nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and α-blockers. NSAIDs and opioids are recommended as the first- and second-line treatments, respectively, under recent guidelines [4,7]. However, these drugs have many side effects and contraindications that require investigation of alternative and adjuvant drugs [7,8].

Ketamine is an anesthetic agent whose analgesic effects have recently been studied for renal colic. Studies have indicated intranasal and injectable ketamine to be effective in treating severe acute pain and renal colic, particularly compared with opioids [7,9]. The primary mechanism of action of ketamine is an antagonistic effect on the N-methyl-d-aspartate (NMDA) receptors. However, the analgesic effects have mainly been attributed to interactions with opioid receptors [10].

Desmopressin is another drug recommended for managing renal colic. Desmopressin is an analog of an antidiuretic hormone that has shown favorable effects with few side effects for treating renal colic in both sublingual and intranasal forms [4,5]. Renal colic results from acute dilatation of urinary tracts along with spasms of smooth muscles at the site of obstruction. This dilatation leads to the release of prostaglandin E2, which causes diuresis by dilating the afferent arterioles and leads to further dilation of urinary tracts [11]. The marked antidiuretic effect of desmopressin is likely responsible for its efficacy in treating renal colic. Furthermore, desmopressin suppresses the contraction of the smooth muscle fibers of the renal pelvis, which might help pain management in renal colic. Likewise, stimulation of β-endorphin release can be effective in the analgesic effects of this drug; however, the mechanisms effective in relieving the pain of renal colic by this drug are still unknown [12,13].

Studies have indicated that patients prefer analgesics with immediate effects and painless administration routes. Common administration routes of analgesics, including oral, intravenous, and intramuscular, have limitations. For instance, oral administration is not common and routine for nothing by mouth patients. Intravenous injection requires the insertion of a peripheral venous catheter by emergency personnel. Intramuscular injection, in addition to pain at the injection site, is associated with delayed onset of drug action and is challenging in obese individuals. The intranasal administration route is favored due to its painlessness, fewer adverse effects, and sufficient effectiveness [9,14,15]. In the present clinical trial study, we investigated the analgesic effect of intranasal ketamine and desmopressin in renal colic patients referred to the ED.

METHODS

Ethics statement
This study was approved by the Research Ethics Committee of Isfahan University of Medical Sciences (No. IR.MUI.MED.REC.1400.191). The study protocol was registered in the Iranian Registry of Clinical Trial (No. IRCT20190422043340N12). Written informed consent was provided by all participants.

Study design and population
This double-blind, randomized clinical trial study was conducted
in Alzahra and Kashani hospital EDs in Isfahan, Iran, from June 2021 to July 2022. Inclusion criteria included the presence of severe renal colic pain (visual analog scale (VAS) > 5 in the flank or abdomen with or without radiating to the groin and genitalia) and a previous history of urolithiasis as diagnosed by an emergency physician. Accompanying symptoms and signs (i.e., dysuria, urine dribbling, and costovertebral angle tenderness) or laboratory findings supporting diagnosis such as hematuria may or may not have been present. Patient age was limited to 18 to 65 years. The diagnosis of renal colic was made based on history, physical examination, and urinalysis. After diagnosis and depending on the need, the presence of renal stones was confirmed in patients using ultrasound or computed tomography. Exclusion criteria were the following: having a history of hypertension, cardiac diseases, peptic ulcer or active gastrointestinal bleeding, chronic hepatic or renal failure, or any drug reaction; being pregnant or lactating; having unstable vital signs (systolic blood pressure < 90 or > 180 mmHg or heart rate < 50 or > 150 beats/min); receiving analgesics in the last 24 hours of hospitalization; loss of consciousness during the survey; and a final diagnosis of other than renal colic.

Randomization and blinding
Patients were randomly assigned to desmopressin, ketamine, or control groups using a computer-generated random number table with four blocks. Medications were prepared daily by an ED nurse based on patients’ codes and labeled A (desmopressin), B (ketamine), or C (control); the labels were blinded to the researcher. The emergency physician who was blinded to the type of agents used a 1-mL syringe in each group to spray the prepared medication (0.5 mL in each nostril) using an intranasal Mucosal Atomization Device (Teleflex Medical). All patients were also blinded to their study group.

Interventions
Desmopressin group patients received intranasal desmopressin at a dose of 40 μg and intravenous ketorolac at 30 mg. In ketamine group patients, intranasal ketamine was administered at a dose of 1 mg/kg and intravenous ketorolac at 30 mg. Control group patients received an intranasal placebo (DB-SALINE 0.9%, DB Pharmacy) and intravenous ketorolac at a dose of 30 mg.

Study protocol
After completing ethics code preliminary requirements and training of emergency physicians, these emergency physicians selected eligible patients to participate in the study. The demographic information including age, sex, and body mass index was recorded. Patients were asked to determine their degree of pain using a VAS on a range of 0 to 10, in which 0 represents no pain and 10 represents the most intense [16]. Pain severity was recorded at baseline and at 10, 30, and 60 minutes after the beginning of the treatment. Vital signs, including heart rate, respiratory rate, and systolic and diastolic blood pressure, were recorded at baseline and at 60 minutes after the beginning of the study. The emergency physician regularly monitored patients during treatment. If the patient’s pain was not reduced effectively (a 50% decrease in VAS score or attainment of a score ≤ 3) after 30 minutes of treatment, 0.1 mg/kg with a maximum dose of 5 mg of morphine was administered as the rescue analgesic and recorded. The primary outcome was the comparative reduction of VAS scores among the three groups after intervention. Secondary outcomes were the occurrence of hemodynamic changes and the need for rescue treatment.

Sample size
Assuming an α of 0.05 and β of 0.2, an 80% statistical power for the study, and final differences between the two test groups of at least 2 points on VAS [6], the necessary sample size was determined to be 40 in each group. To increase the power of study, 45 patients were included in each group.

Statistics analysis
Collected data were analyzed using IBM SPSS ver. 28 (IBM Corp). Frequency and percentage were used to describe qualitative data, and mean and standard deviation (SD) were used to describe quantitative data. Independent t-tests, chi-square tests, repeated measure analysis of variance (ANOVA), and one-way ANOVA were used for inferential analysis.

RESULTS
Enrollment included 135 patients (Fig. 1), their mean ± SD age was 44.1 ± 11.4 years, and 82 (60.7%) were men. All patients who were included in the study had a final diagnosis of renal colic and completed the study. Data from these patients were analyzed. Age, sex, weight, and morphine requirements are compared among the three treatment groups in Table 1.

As indicated in Table 1, the three groups did not have significant differences in age, sex, and weight (P ≥ 0.05). Therefore, the demographic variables were not considered confounders. Also, the need for morphine was similar among the groups (P ≥ 0.05).

Table 2 indicates the mean ± SD of the three groups’ VAS scores
Table 1. Variables in the three groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Desmopressin (n = 45)</th>
<th>Ketamine (n = 45)</th>
<th>Control (n = 45)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>46.2 ± 9.8</td>
<td>43.6 ± 13.7</td>
<td>42.5 ± 10.3</td>
<td>0.294</td>
</tr>
<tr>
<td>Male sex</td>
<td>29 (64.4)</td>
<td>28 (62.2)</td>
<td>25 (55.6)</td>
<td>0.668</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74.8 ± 9.9</td>
<td>76.2 ± 10.1</td>
<td>73.2 ± 9.7</td>
<td>0.889</td>
</tr>
<tr>
<td>History of renal stone</td>
<td>33 (73.3)</td>
<td>35 (77.8)</td>
<td>30 (66.7)</td>
<td>0.493</td>
</tr>
<tr>
<td>Morphine required</td>
<td>8 (17.8)</td>
<td>3 (6.7)</td>
<td>11 (24.4)</td>
<td>0.070</td>
</tr>
</tbody>
</table>

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

Table 2. VAS pain scores between three groups

<table>
<thead>
<tr>
<th>VAS pain score</th>
<th>Group</th>
<th>Difference (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 0 min</td>
<td>Desmopressin (n = 45)</td>
<td>Ketamine (n = 45)</td>
</tr>
<tr>
<td>At 10 min</td>
<td>9.5 ± 0.7</td>
<td>9.4 ± 0.7</td>
</tr>
<tr>
<td>At 10 min</td>
<td>6.7 ± 1.8</td>
<td>5.6 ± 1.2</td>
</tr>
<tr>
<td>At 30 min</td>
<td>4.2 ± 2.2</td>
<td>3.0 ± 1.1</td>
</tr>
<tr>
<td>At 60 min</td>
<td>1.3 ± 1.4</td>
<td>0.9 ± 0.9</td>
</tr>
</tbody>
</table>

P-value = <0.001 <0.001 <0.001 - - -

Values are presented as mean±standard deviation, unless otherwise indicated.

VAS, visual analog scale.

*The mean difference is significant at the 0.05 level. Repeated measure analysis of variance.

During the treatment. The degree of perceived pain of the three groups at baseline was not significantly different (P ≥ 0.05). Pain scores of the patients in the control group were higher than the other two groups at 10, 30, and 60 minutes after the intervention. Therefore, ketamine and desmopressin, along with ketorolac, were superior to ketorolac alone in relieving pain. VAS score dif-
ferences between the ketamine and desmopressin groups compared to the control group were significant at 10, 30, and 60 minutes (P < 0.05). Pain scores in the ketamine group at 10, 30, and 60 minutes were significantly lower than in compared to the desmopressin group (P < 0.05).

No significant differences in vital sign measurements were found among the three groups and between the two intervention groups at 60 minutes after the beginning of the treatment (Table 3). The three groups did not have significant differences in the need for morphine (P ≥ 0.05) (Table 1).

Using repeated measurement ANOVA, we observed that perceived pain scores were significantly reduced in the three groups (Fig. 2 and Table 2).

**DISCUSSION**

Desmopressin is a synthetic replacement for antidiuretic hormone with more powerful and longer-lasting antidiuretic effects. This drug has advantages such as ease of administration and fewer contraindications and side effects than NSAIDs [17,18]. These anti-inflammatory agents can lead to acute kidney failure (AKI) by reducing the glomerular filtration rate (GFR) and renal blood flow in a kidney that is already at risk of failure due to hydronephrosis. Studies have shown that desmopressin exerts its diuretic effects without affecting renal blood flow or GFR. Significant adverse effects of desmopressin, such as hypotension, tachycardia, hyponatremia, and gastrointestinal symptoms, usually resolve within 24 hours after administration and are more noticeable in older patients or with repeated administrations. Our study showed that the patients who received desmopressin did not have a significant difference in vital signs compared to other treatment group patients 1 hour after treatment.

Some human studies investigating desmopressin’s effectiveness on renal colic have had conflicting results. However, most previous studies examined the effects of desmopressin in the short term and were limited to hospitalized patients in the ED [17–19]. In our study, patients receiving desmopressin and ketorolac treatment reported lower pain scores 10, 30, and 60 minutes after the treatment compared to ketorolac alone. Hence, our study confirms the immediate effects of desmopressin in renal colic patients, which is consistent with previous studies [4,5,19]. Arhami Dolatabadi et al. [4] aimed to investigate the effectiveness of intranasal desmopressin on renal colic patients compared to intravenous ketorolac. The pain of the patients who received only desmopressin decreased significantly in the first 10 minutes, as well as the pain of those who received diclofenac. Until the 20th minute, the desmopressin group patients’ pain scores decreased but then tended to rise. Also, during the study, there was no significant difference in the pain scores of patients receiving diclofenac alone and of those receiving diclofenac along with desmopressin. However, at the 30th minute, the VAS scores of patients receiving combination therapy were insignificantly lower. Furthermore, fewer patients receiving combination therapy reported that their pain intensity had not changed [20]. Consistent with Lopes et al. [20], our patients in the desmopressin group had a lower morphine requirement than the controls, though this difference was

### Table 3. Comparison of vital signs before and after intervention

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intervention group</th>
<th>Control group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Desmopressin (n=45)</td>
<td>Ketamine (n=45)</td>
<td>Control group (n=45)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>120.7 ± 6.3</td>
<td>121.8 ± 10.4</td>
<td>119.2 ± 5.1</td>
</tr>
<tr>
<td>Before</td>
<td>121.6 ± 9.9</td>
<td>122.9 ± 11.6</td>
<td>120.4 ± 8.7</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>77.5 ± 4.7</td>
<td>77.9 ± 5.0</td>
<td>76.4 ± 3.5</td>
</tr>
<tr>
<td>Before</td>
<td>78.5 ± 5.4</td>
<td>79.1 ± 6.8</td>
<td>77.7 ± 4.1</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>77.3 ± 6.5</td>
<td>78.3 ± 7.6</td>
<td>77.4 ± 6.3</td>
</tr>
<tr>
<td>Before</td>
<td>79.2 ± 8.5</td>
<td>79.4 ± 8.9</td>
<td>79.4 ± 7.8</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min)</td>
<td>18.6 ± 1.1</td>
<td>19.0 ± 1.5</td>
<td>18.6 ± 1.4</td>
</tr>
<tr>
<td>Before</td>
<td>19.1 ± 1.2</td>
<td>19.2 ± 1.7</td>
<td>19.0 ± 1.5</td>
</tr>
<tr>
<td>Pulse oximetry (%)</td>
<td>95.9 ± 1.7</td>
<td>96.6 ± 1.7</td>
<td>96.2 ± 1.6</td>
</tr>
<tr>
<td>After</td>
<td>94.3 ± 1.9</td>
<td>95.5 ± 1.0</td>
<td>96.0 ± 1.3</td>
</tr>
</tbody>
</table>
| Values are presented as mean ± standard deviation

**Fig. 2.** The differences in visual analog scale (VAS) scores among the three groups at different times.
ketamine to that of ketorolac in relieving pain in patients. Sotoodeh et al. [9, 11] showed that doses of 60 and 120 μg of sublingual desmopressin have equal or greater efficacy than NSAIDs in renal colic patients.

Ketamine is an NMDA receptor antagonist widely used for anesthesia. In recent decades, low-dose ketamine has been used to treat moderate to severe pain [16]. The analgesic mechanisms of this drug are not limited to interactions with NMDA receptors. Studies have shown that ketamine has agonistic effects on opioid receptors, γ-aminobutyric acid receptors, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors, and cholinergic and dopaminergic receptors. However, the analgesic mechanism of this drug is unknown [10]. In recent years, the effectiveness of this drug on renal colic patients has been examined [9, 22–24]. The study of Hosseinejad et al. [7] investigated and compared the effects of intravenous ketamine and morphine on renal colic. The results of this study indicated that the combined treatment of morphine and ketamine was significantly more effective than morphine alone; however, patients receiving ketamine demonstrated more adverse effects and changes in vital signs. In the present study, the vital signs in patients receiving ketamine were not significantly different from other patients; this can be attributed to the intranasal route of administration of ketamine in our study.

Although intravenous ketamine has shown promising analgesic effects, the analgesic effects of intranasal ketamine have been studied in recent years; ketamine has shown favorable effectiveness and few adverse effects in this case [9, 14]. The intranasal form of ketamine reaches a detectable concentration in the blood after 2 minutes and reaches its maximum effects within 30 minutes, which is one of the factors that make this drug suitable for managing renal colic patients [24]. Our study showed that patients receiving intranasal ketamine with intravenous ketorolac had significantly less pain severity than those receiving ketorolac alone or combined with desmopressin throughout the study. Therefore, unlike desmopressin, ketamine has shown favorable results in causing a fast and stable analgesic response. Sotoodehnia et al. [25] investigated and compared the effect of intranasal ketamine to that of ketorolac in relieving pain in patients with renal colic. There was no significant difference in the mean pain scores of the two groups of patients during the study. Similar results were observed in the study of Khavanin et al. [9] in which the mean pain scores of the patients in the intranasal ketamine group were significantly lower in the 5th minute post-treatment. Also, in the study, hospitalization duration and the need for additional analgesics were significantly lower in the ketamine group; patients were significantly more satisfied with their pain relief. In addition, the two groups did not differ significantly in terms of vital signs during the study [9]. Pouraghaei et al. [22] found intranasal ketamine to be as effective as intravenous morphine for pain control in renal colic.

The present study had limitations. This study was a single-center study due to the limited budget. In addition to not recording and investigating non-life-threatening adverse effects of treatments, this study examined the patients only for one hour and can provide no information on long-term outcomes and possible side effects. Also, the changes in VAS cannot be explained by the effects of the study drugs alone because the sample size was small and the effect of ketorolac cannot be ignored. In the control group, patients receiving ketorolac and a placebo also had a significant improvement in their level of pain. To eliminate the effect of ketorolac in future studies, we recommend that ketamine and desmopressin be used as the only drugs.

Despite the limitations, the present study had strengths. Among these strengths was the large sample size and the longer follow-up period compared to previous studies, strengthening our study’s results. Because the ideal analgesic doses of ketamine and desmopressin are not known, we recommend the conduct of multicenter studies with larger sample sizes and longer follow-up duration.

Ketamine had favorable analgesic effects in renal colic patients. Intranasal ketamine had better pain control as compared to intranasal desmopressin, although desmopressin showed efficacy in the first minutes after treatment. The need for rescue treatment in the ketamine group was less than in other groups, but this finding was not statistically significant.

**ARTICLE INFORMATION**

**Author contributions**

Conceptualization: all authors; Data curation: all authors; Formal analysis: FH, AN; Investigation: all authors; Methodology: all authors; Project administration: all authors; Resources: all authors; Supervision: FH, AN; Validation: all authors; Visualization: all authors; Writing—original draft: FH, AN; Writing—review & editing: all authors. All authors read and approved the final manuscript.
**Conflicts of interest**
The authors have no conflicts of interest to declare.

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**Data availability**
Data analyzed in this study are available from the corresponding author upon reasonable request.

**REFERENCES**


Development and demonstration of the protective efficacy of a convertible respiratory barrier enclosure: a simulation study

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²SS-ENG Co Ltd, Bucheon, Korea

Objective The efficacy of previously developed respiratory barrier enclosures to limit healthcare workers’ exposure to aerosols from COVID-19 patients remains unclear; in addition, the design of these devices is unsuitable for transportation or other emergency procedures. Therefore, we developed a novel negative pressure respiratory isolator to improve protection from patient-generated aerosols and evaluated its protective effect in conversion to systemic isolator.

Methods This in vitro study simulated droplets by nebulizing 1% glycerol + 99% ethanol solution. We performed cardiopulmonary resuscitation (CPR) and converted a respiratory barrier enclosure into a systemic isolator with a respiratory barrier as well as a respiratory barrier with negative pressure generator (NPG), which were compared with control and room air. During the procedure, particles were counted for 30 seconds and the count was repeated 10 times.

Results During CPR, the total number of particles in the respiratory barrier with NPG (280,529; interquartile range [IQR], 205,263–359,195; P=0.970) was similar to that in the control (308,789; IQR, 175,056–473,276). Using NPG with a respiratory barrier reduced the number of particles to 27,524 (IQR, 26,703–28,905; P=0.001). Particle number during conversion of the respiratory barrier into a systemic isolator was also lower than in the control (25,845; IQR, 19,391–29,772; P=0.001).

Conclusion The novel isolator was converted to a systemic isolator without air leakage. The aerosol-blocking effect of the isolator was quantified using a particle counter during CPR. Further studies comparing the barrier effect of isolators within various pressure differentials are warranted.

Keywords Infection control; Personal protective equipment; Cardiopulmonary resuscitation; Intubation; Aerosol box

INTRODUCTION

Since the first reported cases of COVID-19, healthcare workers (HCWs) have faced new challenges in resuscitating patients with COVID-19 or those who are at risk but not infected [1]. Approximately 5% to 10% of HCWs who treated patients with COVID-19 have reported being infected with COVID-19 despite the use of personal protective equipment (PPE) [2]. Infected
HCWs are at risk of spreading the infection to other vulnerable individuals, may suffer threats to their own health, and may as a consequence exacerbate their own shortage during severe outbreaks [3,4]. Although the use of PPE is recommended to prevent the spread of COVID-19, demand for it outweighs supply, thus significantly limiting HCW protection [5]. The shortage of PPE and risk of COVID-19 infection in HCWs mandate the need for alternative methods of protection. The plastic shield box, also known as barrier enclosure, aerosol box, or intubation box, is an effective protective device that has been developed for a variety of situations [6,7]. These newly developed devices are designed to protect HCWs and have been shown to be at least partially protective during aerosol-generating procedures, such as endotracheal intubation, extubation, and cardiopulmonary resuscitation (CPR) [6,8]. However, evidence regarding their efficacy in preventing infection and efficiency in various healthcare situations is limited [6,8,9].

During the COVID-19 pandemic, HCW protection is important not only during aerosol-generating medical procedures but also during the transportation of suspected or diagnosed patients for definitive care [10–12]. In addition, reducing the chances of contamination during other emergency procedures, such as coronary angiography, intra-arterial thrombolysis, and bleeding control through gastroscopy in infected patients is important. These considerations for the protection and isolation of HCWs delay definitive emergency treatment of acute myocardial infarction, acute stroke, and abdominal surgery in patients suspected to have COVID-19 [13–15]. However, current barrier enclosures are unsuitable for patient transport and even for performing non-aerosol-generating procedures, such as coronary angiography, intra-arterial thrombolysis of stroke patients, and abdominal surgery [7].

In this study, our board-certified emergency physician– and mechanical engineer–based team aimed to develop a novel negative pressure isolator that is adaptable in various situations and easily convertible to a systemic isolator. We subsequently tested its protective efficacy.

METHODS

Intubation hood with patient access orifices
Our team designed a respiratory isolation hood for intubation and other aerosol-generating procedures using a three-dimensional (3D) design program (Rhinoceros 3D ver. 7.0, McNeel). The height of the patient access orifice was determined according to the physical build of the HCW performing endotracheal intubation. Current aerosol boxes are rectangular [6]; hence, the target location of intubation is difficult to visualize. We considered this limitation and installed a slope from the patient access orifice to the distal portion of the hood accordingly.

Tailored double-layer barrier for chest enclosure
The chest barrier was designed to enclose the patient’s breathing field with the following considerations. First, it was double layered to provide an anteroom structure as in the current negative pressure isolation rooms. Second, rubber bands and drawstrings were used to establish different isolation ranges according to the patient's body size and condition. Finally, the outer layer of the barrier had a Velcro attachment with a polyvinyl chloride (PVC) half-isolator that converted it into a systemic isolator, such as in a conventional cart-type systemic isolator.

Negative pressure generator
In our preliminary study [16], we found that fan-type ventila-
tion machines produced rapid airflow and efficiently contained aerosols with low-pressure differentials compared to room air. We used a previously constructed fan-type ventilation machine that could generate –10 Pa of pressure differential relative to room air and measured such pressure using a sensor (Differential Pressure Transmitter 984, Beck Sensortechnik GmbH). The ventilation machine was called the "negative pressure generator (NPG)." We connected this NPG to the isolator via an 80-mm diameter tube.

Aerosol and droplet simulation
To simulate aerosol and droplets from patients, we used vapor and nebulized droplets. To visualize air flow, an Antari fog machine Model Z-800II (Antari) was used to release buoyant water vapor inside the hood for 10 to 30 seconds. To create droplets, we nebulized 5 mL of a 1% glycerin in 99% ethanol solution next to the mannequin's mouth using an Omron Compressor Nebulizer Model NE-C802 (Omron Healthcare Korea Co Ltd).

Observation and quantification of air leakage during CPR
Air leakage from the isolator was visually observed and quantitatively assessed during CPR. To compare leakage during CPR, the isolator was first filled with vapor, and then a researcher performed CPR under NPG on/off conditions without a chest barrier, with an inner barrier, and with a double-layer barrier. We visually inspected vapor leakage under these six conditions.

To quantify droplet leakage from the isolator, an AeroTrak Portable Particle Counter 9306 (TSI Inc) was positioned next to the CPR operator’s head (80 cm above the bed). This particle counter used a laser diode and a photo detector to count airborne particles within the size ranges of 0.3, 0.5, 1.0, 3.0, and 5.0 µm. The particle counter was set up to analyze droplets by aspirating 2.8 L of air every 30 seconds. One researcher performed chest compressions for 30 seconds without a chamber (control), with a chamber (chamber condition), and with chamber-operating NPG (NPG condition) and the experiment was repeated 10 times for each condition (Supplementary Fig. 1).

Observation and quantification of air leakage during conversion
Aerosol and droplet containment during isolator conversion was also examined. Two researchers converted the respiratory barrier enclosure into a systemic isolator while operating NPG, while another researcher utilized the particle counter at the same position as that used during the CPR.

Statistical analysis
In the pilot test, the difference between baseline of particles in regular room air and those in the air after nebulizing for 2 minutes was calculated, and the mean difference of particles was 268,168 ± 204,952. The sample size for the detection of 1% mean difference in 2,682 ± 2,050 particles with a two-sided significance level of 5% and power of 95% was 7; therefore, particle count was performed 10 times for each condition. To test the normality in each condition, Shapiro-Wilk test was conducted, and the difference between the groups was analyzed using an independent t-test when normality was satisfied, and Mann-Whitney U-test when normality was not satisfied. All statistical analyses were performed using SAS ver. 9.4 (SAS Inc). A P-value of < 0.05 was considered statistically significant.

RESULTS

Intubation hood and tailored double-layer barrier for the chest
We fabricated a mock-up of the hood (Fig. 1) and the double-layer barrier structure (Fig. 2) to test the newly designed device. The height of the hood was approximately 500 mm and that of the patient access orifices was 380 mm. This difference in height formed an inclined plane in the visual field of the operator. This design facilitated the procedure by providing the operator a closer view of the patient’s larynx. The intubation hood had two other patient access orifices for the assistant or various connectors for oxygen or medications.

The double-layer barrier was made of a coated waterproof fabric. The inner layer could be secured to the patient’s chest using a rubber (latex-free) band and the Velcro fixer (Fig. 2A), and the

Fig. 1. The three-dimensional (3D) design of (A) the intubation hood and (B) the mock-up. (A) The Rhinoceros 3D ver. 7.0 (McNeel) is used to design the intubation hood with the appropriate height and width for intubation and computed tomography scans. (B) The hood mold was built using a transparent acrylic resin.
Efficient covertible respiratory barrier

Fig. 2. Double-layer barrier made of a waterproof fabric on the side of the patient. (A) The inner layer of the double-layer barrier is secured to the patient's chest using a rubber band and a Velcro fixer. (B) Changeable outer layer of the double-layer barrier secured using a drawstring and stopper. (C) Converted systemic isolator. The outer layer is equipped with a Velcro attachment (arrow) with the polyvinyl chloride half-isolator to convert it into a full body isolator.

changeable outer layer could be secured anywhere between the patient's chest and waist using the drawstring (Fig. 2B). The space between the two barriers prevented internal air leakage during chest compressions or postural changes and maintained the internal negative pressure.

The outer layer also had a Velcro attachment with the PVC half-isolator for converting the respiratory barrier enclosure to a systemic isolator. The presence of the inner layer during this conversion prevented air leakage and maintained negative pressure in the intubation hood (Fig. 2C).

Observation and quantification of air leakage during CPR
The generated vapor filled the isolator in 10 seconds. Without the double-layer barrier, most of the vapor escaped from the intubation hood within the first 30 seconds of the test. After the inclusion of the inner layer, the vapor in the intubation hood escaped to a lesser extent. However, during chest compressions, considerable vapor leakage was evident from the patient-layer connection (Fig. 3A). After the inclusion of the outer layer, vapor leakage was diminished but still obvious (Fig. 3B). When the NPG was operated to achieve an isolator pressure of approximately 10 Pa less than room air pressure, a small amount of vapor leaked from the inner layer (Fig. 3C), but no leakage was evident from the outer layer even after performing chest compressions (Fig. 3D and Supplementary Video 1). No visible vapor leakage was evident when the respiratory barrier enclosure was converted to a full body isolator while operating the NPG (Fig. 4 and Supplementary Video 2).

The nebulizer generated 200,000 to 300,000 particles. To quantitatively assess the efficacy of droplet containment by the isolator, we conducted nebulization without the isolator and measured the airborne particle count. This served as a comparative baseline and was labeled as the nebulizer (control). The total number of particles in the control group (308,789; interquartile range [IQR], 175,056–473,276; P = 0.001) was significantly higher than that in room air (19,664; IQR, 18,088–21,562) (Supplementary Table 1). Applying a respiratory barrier enclosure with a double-layer barrier significantly reduced the total number of particles in the air by 25,275 (IQR 22,214–8,905; P = 0.001). However, during chest compressions, the total number of particles in the air was not significantly decreased (280,529; IQR, 205,263–359,195; P = 0.970), in contrast to when the NPG was in use (27,524; IQR, 26,703–28,905; P = 0.001) (Table 1). This result shows that a respiratory barrier enclosure with negative pressure (–10 Pa) could reduce aerosol and droplet transfer from the patient to the CPR performer.

However, lower particle count measured compared to the control does not imply complete containment. If the isolator completely blocked particle escape, there should have been no increase in particle quantity when compared to the baseline particle count of room air with the nebulizer placed inside. When compared with the baseline particle level in room air (baseline), the total number of particles in the air increased even when using the respiratory barrier enclosure with NPG during CPR (27,722 ± 1,239 vs. 21,125 ± 3,245, P = 0.001) (Table 2).

Observation and quantification of air leakage during conversion
Most of the vapor inside the respiratory barrier enclosure was removed within 15 seconds using an NPG. We also attempted to measure the air-cleaning time in the systemic isolator, since the presence of the inner layer caused some difficulties in transferring the generated vapor from the intubation hood to the PVC half-isolator. After the vapor was generated, most of it was removed from the systemic isolator in 120 seconds (Supplementary Video 3).

The total quantity of particles counted after the conversion of
Fig. 3. Vapor leakage during chest compressions. (A) Inclusion of the inner layer and chest compression procedure. There is considerable vapor leakage (arrows) at the patient-inner layer interface. (B) Inclusion of the outer layer decreases the amount of vapor leakage, but it continues to persist. (C) Inclusion of the inner layer with negative pressure decreases the amount of vapor leakage (arrow) compared with that in (A). (D) After the inclusion of the outer layer with negative pressure, there is no vapor leakage visible even after performing chest compressions.

Fig. 4. Respiratory barrier enclosure converted into a systemic isolator. (A) Velcro connection (arrow) between the base of the outer layer and polyvinyl chloride (PVC) half-isolator. (B) Velcro attachment at each sidewall (arrow). (C) Closing the midline zipper. (D) Systemic isolator (arrow, Velcro attachment site).
Efficient convertible respiratory barrier

Table 1. Comparison of the number of particles around the airway of the CPR operator with the number of particles in the control

<table>
<thead>
<tr>
<th></th>
<th>Without CPR</th>
<th></th>
<th>With CPR</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Respiratory</td>
<td>Nebulizer&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Respiratory</td>
<td>Nebulizer&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>barrier</td>
<td>(control)</td>
<td>barrier</td>
<td>(control)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.01</td>
<td>0.01</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>308,789</td>
<td>(175,056–473,276)</td>
<td>308,789</td>
<td>(175,056–473,276)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>25,263 ± 3,766</td>
<td></td>
<td>280,529</td>
<td>(205,263–359,195)</td>
<td>0.970</td>
</tr>
<tr>
<td></td>
<td>(22,214–28,905)</td>
<td></td>
<td>27,524</td>
<td>(26,703–28,905)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range).

CPR, cardiopulmonary resuscitation; NPG, negative pressure generator.

<sup>a</sup>Without isolator.

Table 2. Comparison of the number of particles around the airway of the CPR operator with the number of particles in the room air

<table>
<thead>
<tr>
<th></th>
<th>Without CPR</th>
<th></th>
<th>With CPR</th>
<th></th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Respiratory</td>
<td>Baseline (room air)</td>
<td>Respiratory</td>
<td>Baseline (room air)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>barrier</td>
<td></td>
<td>barrier</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.017</td>
<td>0.010</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>21,125 ± 3,245</td>
<td>25,106 ± 3,109</td>
<td>27,722 ± 1,239</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

CPR, cardiopulmonary resuscitation; NPG, negative pressure generator; SD, standard deviation; IQR, interquartile range.

The groups were analyzed using an independent t-test when normality was satisfied, and Mann-Whitney U-test when normality was not satisfied.

DISCUSSION

This in vitro simulation study reported the development and assessment of a convertible respiratory barrier enclosure with an intubation hood and a double-layer barrier. This isolator should protect HCWs from respiratory infection during airway and non-airway management as well as during patient transport. The device was effective in blocking aerosols and droplets from the patient’s respiratory tract, and this protective effect was maintained during chest compressions, and during conversion to a systemic isolator. Once this device is correctly applied to a patient, it can be used for transportation and other procedures, enabling the performance of emergency procedures even in an environment without isolation facilities.

This novel isolator has properties that allow it to overcome several disadvantages of previous barrier enclosures. It has four large patient access orifices for the full range of motion of the operator’s arm and it has separate spaces to prevent aerosol leaks during procedures. Our device is more comfortable to use than the aerosol box and is associated with a lower risk of destroying PPE during operation [18,19]. Additionally, the opening-type patient access orifices offer improved patient access compared to those used in the enclosure type [8,20].

The double-layer barrier is associated with a lower risk of air leakage. We found that a single layer barrier could not contain vapor with a low-pressure difference. This demonstrates the need for a double-layer barrier (Fig. 3). In addition, most current barrier enclosures were designed with a head cover and patient access orifices in mind, but with no consideration for enclosing other body areas [8]. Consequently, a protective effect for the operator performing intubation was evident, while no protective effect for the patient was observed [7]. Therefore, the use of such barrier enclosures is limited to during intubation and other aerosol-generating procedures. However, in this study, our novel double-layer barrier had a protective effect on the patient body side. Hence, it is feasible to use this device during other procedures and to utilize it instead of an isolation room. Our novel isolator can also be converted into a conventional negative pressure cart for patient...
transportation and vice versa without aerosol leakage. This conversion can provide increased protection for HCWs during patient transport for emergency procedures or for in-hospital transport. In addition, a variety of invasive procedures such as endoscopy and angiography could be performed without getting on and off the converter.

This novel isolator uses a high-flow fan-type air circulator to create a negative pressure environment in the enclosure. It differs from other enclosures using wall suction or other types of vacuum pumps [6–8,20]. In addition, the pressure difference between room air and the isolator was verified considering patient safety and the effect of air suctioning on the patient. Furthermore, we also observed that a pressure difference of approximately 10 Pa was sufficient to contain the aerosol and to quickly remove the particles in the air from inside the isolator.

This isolator has potential limitations. First, its intubation hood is relatively heavy, making it difficult for one HCW to secure the device to the patient’s head. Hence, this could lead to accidents during the quarantine period. However, our test hood was a mock-up model, and the thickness of the hood was not considered. A heavy hood can be addressed by fabricating a lighter hood with thinner walls. Second, we did not test for air leakage from the air circulator. Our team used a high-efficiency particulate air filter with a 0.3-µm filter and 99.7% efficacy, under the assumption that it would not leak. Depending on the type of filter or method of application, the infected air can contaminate the room. Third, the size of our device may be inadequate for patients with obesity and those with broad shoulders. However, our intubation hood is approximately 500 mm in width and height, which is suitable for bed size, and can even be fitted into a computed tomography machine. Fourth, although we clarified that the pressure difference of approximately 10 Pa was sufficient to reduce air contamination, there is limited evidence about proper pressure differential for the containment of aerosol and droplets without harmful effects on patients. Further studies must be conducted to compare the barrier effects of isolators within various pressure differential conditions and to clarify optimal pressure differential. Fifth, although the double-layer barrier with negative pressure showed high efficacy in aerosol containment, a small amount of particle leakage was detected during CPR, compared to the baseline room air. This indicates that there is room for improvement in the protective efficacy, and further studies are needed to enhance containment measures. However, when comparing each group based on particle size, it was observed that the smaller the particle, the more leakage occurred. When operating

NPG, whether during CPR or conversion, the number of particles larger than 3 µm was not significantly different from that in the baseline room air (during CPR: 3 µm, $P = 0.075$; 5 µm, $P = 0.336$; 10 µm, $P = 0.214$; during conversion: 3 µm, $P = 0.724$; 5 µm, $P = 0.255$; 10 µm, $P = 0.718$) [Supplementary Table 2]. Considering that the average size of patient droplets is about 2 to 3 µm, the observed containment of particles larger than 3 µm is sufficient to protect HCWs from airborne diseases. Sixth, this study focuses on the development of a convertible isolator, capable of transforming from a whole-body isolator to a hood-type barrier. This implies that the containment efficacy of this novel isolator must be compared not only with hood-type isolators but with other transportation chambers as well. However, there is currently no available published data about transportation isolators, except for pressure information and filter efficacy. As a result, we were not able to directly compare the containment efficacy of our novel isolator with these types of isolators. However, the new development type isolator may have comparable containment efficacy, along with a high-efficiency particulate air (HEPA) filter (99.7%), which could negate the need for comparison with other chamber’s efficacy. Further study is needed to accurately and quantitatively measure the containment efficacy itself. Finally, this study is only a simulation; thus, further studies are needed to confirm its applicability on real patients. In addition, considerations on the efficiency of performing procedures with the hood are needed. Therefore, simulation studies addressing the efficiency and limitations when performing procedures with this novel isolator must be conducted in the future. Aerosol dispersal during application and removal of the chamber, similar to donning or doffing PPE, especially needs to be investigated.

In summary, we developed a novel negative pressure isolator that included an intubation hood with patient access orifices, a double-layer barrier, and an efficient NPG with an air circulator and pressure detector. This novel isolator can be converted to a systemic isolator without air leakage. We quantified the aerosol-blocking effect of the isolator using a particle counter during aerosol-generating procedures. Future studies addressing the efficiency and limitations when performing procedures using our novel isolator and comparing the barrier effect of isolators within various pressure differential are warranted. We anticipate that this novel isolator can be used for the treatment of infected patients without the risk of infection. It is expected to be highly beneficial in coping with potential hazardous infectious diseases following COVID-19.
ARTICLE INFORMATION

Author contributions
Conceptualization: JYH, KSS; Data curation: MHP; Formal analysis: JYH; Funding acquisition: JYH; Investigation: MHP, JWM; Methodology: JHK, MHP, JYH; Project administration: KSS, JYH; Resources: KSS; Supervision: JYH; Validation: KSS; Visualization: KSS; Writing–original draft: MHP, JYH; Writing–review & editing: all authors. All authors read and approved the final manuscript.

Conflicts of interest
The methods used in this study is currently under patent pending in Korea (No. 10-2021-0072895), and the authors may receive remuneration if the technology is transferred. However, it has not yet been commercialized, the authors have not received any financial benefit from this study. The authors have no other conflicts of interest to declare.

Funding
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Acknowledgments
The authors thank Crenvitec Co Ltd (Gwangju, Korea) for granting access to the use of the particle counter.

Data availability
Data analyzed in this study are available from the corresponding author upon reasonable request.

Supplementary materials
Supplementary Table 1. Count of particles in room air with or without droplet generation
Supplementary Table 2. Comparison of large-sized particles around the airway of the CPR operator and that of room air
Supplementary Fig. 1. Researcher’s position during cardiopulmonary resuscitation (CPR) (A) without an isolator and (B) with an isolator.
Supplementary Video 1. Air leakage during chest compression. (A) Inner layer with negative pressure. (B) Double layer without negative pressure. (C) Double layer with negative pressure. Application of negative pressure in the double-layer barrier stops vapor leakage during chest compressions.
Supplementary Video 2. The entire sequence of conversion from the respiratory barrier enclosure to a systemic isolator. The total procedural time is 70 to 90 seconds. No vapor leakage is evident during conversion with the negative pressure generator.

REFERENCES


Clinical characteristics and outcomes of injuries in agricultural and nonagricultural workers visiting the emergency department: a propensity-matched analysis

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Objective Agriculture is a hazardous industry. However, previous studies have focused on injuries to agricultural workers without comparison with injuries to nonagricultural workers. Therefore, we compared the clinical characteristics and outcomes of injuries reported at an emergency department (ED) between agricultural workers and nonagricultural workers.

Methods We established a prospective ED-based agricultural injury surveillance system at a tertiary university hospital. Adult patients visiting the ED for an injury were divided into farmer and non-farmer groups depending on their engagement with agriculture. Using an adjusted multivariate analysis and propensity score matching (age, sex, inhabitant, and insurance type), we compared the clinical characteristics and outcomes of injuries between the farmer and non-farmer groups.

Results In total, 38,556 injured adult patients (37,746 in the non-farmer group and 810 in the farmer group) were available for the unmatched sample analysis. The 1,620 matched subjects were equally classified after one-to-one nearest-neighbor propensity score matching. A multivariate logistic regression analysis of the unmatched sample revealed higher adjusted odds ratios (ORs) for intensive care unit admission (adjusted OR, 1.752; P=0.003) and overall surgery (adjusted OR, 1.870; P<0.001) in the farmer group. In contrast, univariate logistic regression analyses of the propensity score–matched sample found a higher OR in the farmer group only for overall surgery (OR, 1.786; P<0.001).

Conclusion Injuries of agricultural workers had higher odds only of requiring surgery; differences in injury-related mortality between groups were not statistically significant in either the matched or unmatched sample analyses.

Keywords Occupational injuries; Wounds and injuries; Farmers; Propensity score; Agriculture
INTRODUCTION

Agriculture is an essential industry that meets the basic needs of society, and it employs the largest number of workers globally among all industries [1]. Although the industrial structure and population distribution in Korea have changed since the advent of modern industry, agriculture remains the main industry in many provinces, with about 2.3 million farmers engaged in agriculture in 2020 [2].

Acute injuries among agricultural workers have consistently been ranked as among the highest in all industries, along with transportation and construction [3–5]. In addition, fatality rates for agricultural workers in many countries, including the United States, European Union members, and Korea, are invariably several times greater than the average rate for all industries combined [6–8].

In 2019, approximately 22.2 million full- and part-time workers were employed in the production agriculture and food industries in the United States. About 410 farmers and farm workers died from a work-related injury, resulting in a fatality rate of 19.4 deaths per 100,000 full-time workers in the United States in 2019 [8].

According to the Korean Farmers’ Occupational Disease and Injury Survey, 48,405 farmers suffered an injury that required more than 1 day of absence from work during the previous year. The estimated prevalence of injuries among Korean farmers was 2.7% in 2019 [9].

Although agricultural workers are thus at a very high risk for fatal and nonfatal injuries, few studies of health and safety in the agricultural setting have been done until recently. Injuries to agricultural workers stem from a complex chain of inherent factors, including human (cultural), environmental, and agent factors [10,11]. It is therefore imperative to study the unique epidemiology of injuries to agricultural workers and compare it with injuries to workers in other industries. However, most previous studies focused only on agricultural workers as the study population, with relatively few studies directly comparing agricultural workers with workers in other industries [12–17]. Therefore, information about the clinical aspects of injuries to agricultural workers, distinct from other industries’ workers, remains unclear due to a lack of appropriate data sources.

In this study, we set out to compare the clinical characteristics and outcomes of injuries between agricultural workers and non-agricultural workers who visited an emergency department (ED) by establishing a prospective ED-based agricultural injury surveillance system (ED-AgISS).

METHODS

Ethics statement

This study was reviewed and approved by the Institutional Review Board of Jeju National University Hospital (No. 2018-07-011), with a waiver for the need to obtain informed consent.

Study design and setting

We conducted a retrospective analysis of data from the prospective ED-AgISS registry created for the Safety from Agricultural Injury to Farmers (SAIF) study at a tertiary university hospital. SAIF is a comprehensive community- and hospital-based study investigating the occupational and environmental exposures that affect the epidemiology of agricultural injury and its outcomes among farmers residing on Jeju Island. SAIF is supported by the Jeju Center for Farmers’ Safety and Health of the Ministry of Agriculture, Food, and Rural Affairs of Korea.

The ED-AgISS was designed as an additional module of the existing ED-based Injury Surveillance System (EDISS) and was in-
tended to provide in-depth occupational injury surveillance for agricultural workers. The Korean Centers for Disease Control and Prevention established the EDISS in 2006 as a nationwide, multi-center prospective registry to investigate general injury epidemiology at 23 EDs in tertiary hospitals [18].

The ED-AgISS was implemented in October 2015 as a two-step in-depth injury surveillance system focused on farmers’ occupational injuries. Details in the registry information (standard and expanded datasets) are collected differently depending on occupation (farmers and non-farmers).

Selection of participants
Our eligible study population consisted of all injured adult patients who visited the ED of Jeju National University Hospital (Jeju, Korea) between October 1, 2015, and December 31, 2020. The diagnostic codes of the eligible population were consistent with "injury, poisoning, and certain other consequences of external cause (S00–T88)" in the International Classification of Diseases, 10th Revision [19].

The included study population was 18 years or older on the day of the incident and was divided into farmer and non-farmer groups. Patients who died upon arrival at the ED or whose injury severity or final clinical outcome could not be determined were excluded from the final analysis.

Data collection
The primary purpose of the ED-AgISS is to capture the occupation (farmers vs. non-farmers) of injured patients who visit the ED with the omission of as few cases as possible. Therefore, independent investigators from the Jeju Center for Farmers’ Safety and Health at Jeju National University Hospital confirmed patient status regarding engagement in agricultural work for all injured patients.

The ED-AgISS registry collects comprehensive information in the following domains using a two-step injury surveillance system: (1) a standard dataset for general injury epidemiology from EDISS and (2) an expanded dataset to establish occupational injury epidemiology among agricultural workers. After routinely obtaining standard EDISS data from all injured patients who visit the ED in the first step, ED staff collected expanded data about injured patients confirmed to be engaged in agricultural work in the second step.

The standard dataset from EDISS includes sociodemographic (age, sex, insurance type, vital signs, and mental status), injury characteristics (intention, mechanism, activities, places, emergency medical service [EMS] usage, and whether the injury was alcohol related), diagnosis, injury severity index (Revised Trauma Score [RTS], Injury Severity Score [ISS]), emergency care process with a time log, treatment, and disposition at the hospital (discharge, interhospital transfer, admission, death) [18].

The expanded dataset contains the characteristics of injuries to agricultural workers based on the occupational injury and illness classification system and agricultural work-related conditions (type of farming, total farming career experience, in-depth category of places, protective devices, and agricultural machinery) (Supplementary Material 1) [20].

Outcomes of interest
Our primary outcome measures in this study were binary indicators of in-hospital 7-day mortality, 14-day mortality, and overall injury-related mortality. The secondary outcomes were indication for surgery (yes or no) within the first 72 hours and admission to the intensive care unit (ICU), which reflects the urgent need for special medical resources.

Statistical analysis
We estimated the propensity scores of each participant using a multivariate logistic regression model for the odds of being allocated to the farmer or non-farmer group, in which the baseline demographics (age, sex, inhabitant, and insurance type) and year of injury were the predictors for the matching criteria. Because of the temporal order associated with a causal relationship, only variables prior to the injury incident were considered as predictors.

We matched each patient in the farmer group with a patient in the non-farmer group using propensity scores calculated with one-to-one nearest-neighbor matching without replacement and within a caliper size of 0.2, which resulted in pairs of patients in the matched sample. Numerical and graphical diagnostics were performed to compare the extent of balance between the two groups in the dataset before and after propensity score matching [21,22]. For each variable used in the matching process, we performed the following analyses: t-tests to compare the equality of means in the two samples, the standardized percentage bias before and after matching with the achieved percentage reduction, and the variance ratio of the farmer group to the non-farmer group. We also calculated the following overall measures of covariate imbalance before and after propensity score matching: pseudo R2 from the probit estimation of the conditional treatment probability (propensity score) for all the variables, with the corresponding P-values from the likelihood ratio test of the joint insignificance of all the regressors; the mean bias as a summary
indicator of the distribution of the absolute bias; Rubin’s B (the absolute standardized difference of the means of the linear index of the propensity score in the treated and nontreated groups); and Rubin’s R (the ratio of treated to nontreated variances of the propensity score index). If B was less than 25 and R was between 0.5 and 2 for the samples, the groups were considered sufficiently balanced [23].

We calculated descriptive statistics for the baseline demographics, injury epidemiology, and clinical outcomes of the study population stratified by occupation (farmers and non-farmers) before and after propensity score matching. The descriptive statistics are presented as frequencies and percentages for categorical variables and as means ± standard deviations or medians with interquartile ranges for continuous variables, depending on the distribution.

Univariate analyses were conducted between the two groups in both the unmatched and matched samples for each baseline demographic variable, injury epidemiology, and clinical outcomes using Student t-test, Wilcoxon rank-sum test, chi-squared test, or Fisher exact test, as appropriate.

In the unmatched sample, a multivariate logistic regression analysis adjusted for age, sex, inhabitant, insurance type, and year of injury was used to identify whether occupation affected the dichotomous primary and secondary outcomes between the farmer and non-farmer groups. A secondary analysis using a bivariate logistic regression was used in the propensity score–matched sample to identify the relationships between occupation and the outcomes of interest.

All statistical analyses were performed in Stata ver. 17.0 (StataCorp). All tests were two-tailed, and the statistical significance level was < 0.05.

RESULTS

Study population flow

Fig. 1 illustrates the overall flow of the study population. Adult patients (18 years or older) who visited the ED due to trauma from October 2015 to December 2020 were eligible for this study. Among the 38,691 injured adult patients who visited the ED in that time, 135 were excluded because of missing data, leaving 38,556 subjects (37,746 in the non–farmer group and 810 in the farmer group) for the unmatched sample analysis and propensity score matching. After one-to-one nearest-neighbor propensity score matching, the 1,620 matched subjects were equally classified into the two groups (non-farmers and farmers).

Baseline demographics

Table 1 provides a comparison of the baseline demographics between the farmer and non-farmer groups before and after propensity score matching. In the unmatched sample, the patients’ demographics prior to the injury event differed significantly between the groups (farmer vs. non-farmer) in terms of sex (female sex, 37.3% vs. 44.3%), age (61.1 ± 13.2 years vs. 47.6 ± 18.8 years), inhabitant (visitors, 1.6% vs. 16.5%), insurance type (auto insurance, 4.8% vs. 18.6%), and distribution in the year. In addition, we found statistically significant differences in demographics related to the injury, such as alcohol-relatedness of the injury, EMS usage, AVPU (alert, verbal, pain, unresponsive) mental status, Glasgow Coma Scale (GCS) score, systolic blood pressure < 90 mmHg, and disposition (P < 0.05).

After propensity score matching, several of the differing baseline demographics (age, sex, inhabitant, insurance type, and year of injury) were balanced in the matched sample. After matching, alcohol-related injury and disposition still differed significantly, but EMS usage, AVPU mental status, GCS score, and systolic blood pressure < 90 mmHg no longer differed significantly between farmers and non-farmers.

Injury characteristics

The injury characteristics in the farmer and non-farmer groups before and after matching are presented in Table 2. In both the
unmatched and propensity score–matched samples, most of the injury characteristics differed between the two groups. After matching, the trend for group differences in the distribution of injury characteristics persisted and even became more pronounced. In particular, injured patients in the farmer group were more likely than those in the non-farmer group to have an accidental injury, cut or penetrating injury, injury that occurred during paid work activity, injury that occurred in an outdoor workspace, and a temporal incidence pattern involving non-winter, weekend, and daytime injuries. On the other hand, injured patients in the non-farmer group were more likely than those in the farmer group to have an intentional violent injury, fall or slip as the mechanism of injury, injury during vital or unpaid work activity, injury occurring indoors in the home or residence, and a temporal incidence pattern involving winter, weekday, and other than daytime injuries.

Injury severity and clinical outcomes
The descriptive statistics for injury severity and clinical outcomes are presented in Table 3, and the odds ratios (ORs) for clinical

Table 1. Baseline demographics of injured patients by occupation (farmers and non-farmers)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unmatched sample (n = 38,556)</th>
<th>Matched sample (n = 1,620)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-farmer (n = 37,746)</td>
<td>Farmer (n = 810)</td>
</tr>
<tr>
<td>Female sex</td>
<td>16,725 (44.3)</td>
<td>302 (37.3)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>47.6 ± 18.8</td>
<td>61.1 ± 13.2</td>
</tr>
<tr>
<td>Inhabitant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resident</td>
<td>31,511 (83.5)</td>
<td>797 (98.4)</td>
</tr>
<tr>
<td>Visitor</td>
<td>6,235 (16.5)</td>
<td>13 (1.6)</td>
</tr>
<tr>
<td>Insurance type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>National health insurance</td>
<td>28,218 (74.8)</td>
<td>743 (91.7)</td>
</tr>
<tr>
<td>Medicare</td>
<td>1,773 (4.7)</td>
<td>13 (1.6)</td>
</tr>
<tr>
<td>Auto insurance</td>
<td>7,031 (18.6)</td>
<td>39 (4.8)</td>
</tr>
<tr>
<td>Self-pay (uninsured)</td>
<td>671 (1.8)</td>
<td>15 (1.9)</td>
</tr>
<tr>
<td>Other</td>
<td>53 (0.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>1,725 (4.6)</td>
<td>35 (4.3)</td>
</tr>
<tr>
<td>2016</td>
<td>7,519 (19.9)</td>
<td>235 (29.0)</td>
</tr>
<tr>
<td>2017</td>
<td>7,607 (20.2)</td>
<td>208 (25.7)</td>
</tr>
<tr>
<td>2018</td>
<td>7,353 (19.5)</td>
<td>124 (15.3)</td>
</tr>
<tr>
<td>2019</td>
<td>7,405 (19.6)</td>
<td>119 (14.7)</td>
</tr>
<tr>
<td>2020</td>
<td>6,137 (16.3)</td>
<td>89 (11.0)</td>
</tr>
<tr>
<td>Alcohol related</td>
<td>3,262 (8.6)</td>
<td>16 (2.0)</td>
</tr>
<tr>
<td>EMS use (yes)</td>
<td>10,739 (28.5)</td>
<td>275 (34.0)</td>
</tr>
<tr>
<td>AVPU mental status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alert</td>
<td>37,220 (98.6)</td>
<td>793 (97.9)</td>
</tr>
<tr>
<td>Verbal response</td>
<td>294 (0.8)</td>
<td>3 (0.4)</td>
</tr>
<tr>
<td>Painful response</td>
<td>163 (0.4)</td>
<td>9 (1.1)</td>
</tr>
<tr>
<td>Unresponsive</td>
<td>69 (0.2)</td>
<td>5 (0.6)</td>
</tr>
<tr>
<td>Glasgow Coma Scale</td>
<td>14.9 ± 0.7</td>
<td>14.9 ± 1.1</td>
</tr>
<tr>
<td>Vital sign</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>142.4 ± 21.5</td>
<td>146.7 ± 24.2</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>84.2 ± 13.5</td>
<td>84.5 ± 14.2</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>81.9 ± 14.2</td>
<td>77.3 ± 13.7</td>
</tr>
<tr>
<td>Respiration rate (breaths/min)</td>
<td>20.0 ± 1.5</td>
<td>20.0 ± 1.6</td>
</tr>
<tr>
<td>BP &lt; 90 mmHg</td>
<td>126 (0.3)</td>
<td>9 (1.1)</td>
</tr>
<tr>
<td>Disposition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharge from ED</td>
<td>31,210 (82.7)</td>
<td>496 (61.2)</td>
</tr>
<tr>
<td>Discharge from ward</td>
<td>5,602 (15.4)</td>
<td>294 (36.3)</td>
</tr>
<tr>
<td>Transfer</td>
<td>555 (1.5)</td>
<td>14 (1.7)</td>
</tr>
<tr>
<td>Death</td>
<td>126 (0.3)</td>
<td>6 (0.7)</td>
</tr>
<tr>
<td>Other</td>
<td>53 (0.1)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Values are presented as number (%) or mean±standard deviation.
EMS, emergency medical services; AVPU, alert, verbal, pain, unresponsive; SBP, systolic blood pressure; DBP, diastolic blood pressure; ED, emergency department.

*a*Used for propensity score matching.
Table 2. Characteristics of injured patients by occupation (farmers and non-farmers)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Unmatched sample (n = 38,556)</th>
<th>Matched sample (n = 1,620)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-farmer (n = 37,746)</td>
<td>Non-farmer (n = 810)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Farmer (n = 810)</td>
<td>Farmer (n = 810)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Intention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accidental</td>
<td>34,707 (92.0)</td>
<td>778 (96.1)</td>
<td>748 (92.4)</td>
</tr>
<tr>
<td>Self-harm</td>
<td>840 (2.2)</td>
<td>29 (3.6)</td>
<td>17 (2.1)</td>
</tr>
<tr>
<td>Assault or violence</td>
<td>1,916 (5.1)</td>
<td>0 (0)</td>
<td>39 (4.8)</td>
</tr>
<tr>
<td>Unknown</td>
<td>283 (0.7)</td>
<td>3 (0.3)</td>
<td>6 (0.7)</td>
</tr>
<tr>
<td>Injury mechanism</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Fall or slip down</td>
<td>10,736 (28.4)</td>
<td>214 (26.4)</td>
<td>371 (45.8)</td>
</tr>
<tr>
<td>Motor vehicle collision</td>
<td>8,504 (22.5)</td>
<td>83 (10.2)</td>
<td>70 (8.8)</td>
</tr>
<tr>
<td>Blunt by objects</td>
<td>6,433 (17.0)</td>
<td>130 (16.1)</td>
<td>124 (15.3)</td>
</tr>
<tr>
<td>Cut or penetrating</td>
<td>4,627 (12.3)</td>
<td>169 (20.9)</td>
<td>66 (8.2)</td>
</tr>
<tr>
<td>Other</td>
<td>7,446 (19.7)</td>
<td>214 (26.4)</td>
<td>179 (22.1)</td>
</tr>
<tr>
<td>Place</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Indoor</td>
<td>14,092 (37.3)</td>
<td>69 (8.5)</td>
<td>335 (41.4)</td>
</tr>
<tr>
<td>Outdoor</td>
<td>19,293 (51.1)</td>
<td>681 (84.1)</td>
<td>375 (46.3)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4,361 (11.5)</td>
<td>60 (7.4)</td>
<td>100 (12.3)</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Home or residence</td>
<td>10,968 (29.1)</td>
<td>49 (6.1)</td>
<td>298 (36.8)</td>
</tr>
<tr>
<td>Road</td>
<td>10,296 (27.3)</td>
<td>76 (9.4)</td>
<td>158 (19.5)</td>
</tr>
<tr>
<td>Commercial area</td>
<td>3,194 (8.5)</td>
<td>6 (0.7)</td>
<td>55 (6.8)</td>
</tr>
<tr>
<td>Work place</td>
<td>3,230 (8.6)</td>
<td>530 (65.4)</td>
<td>100 (12.4)</td>
</tr>
<tr>
<td>Hospital</td>
<td>514 (1.4)</td>
<td>0 (0)</td>
<td>10 (1.2)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>9,544 (25.3)</td>
<td>149 (18.4)</td>
<td>189 (23.3)</td>
</tr>
<tr>
<td>Activity</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Paid work</td>
<td>5,419 (14.4)</td>
<td>729 (90.0)</td>
<td>154 (19.0)</td>
</tr>
<tr>
<td>Unpaid work</td>
<td>15,881 (41.5)</td>
<td>27 (3.3)</td>
<td>235 (29.0)</td>
</tr>
<tr>
<td>Activities of daily living</td>
<td>10,494 (27.8)</td>
<td>32 (4.0)</td>
<td>316 (39.0)</td>
</tr>
<tr>
<td>Leisure or play</td>
<td>1,407 (3.7)</td>
<td>1 (0.1)</td>
<td>18 (2.2)</td>
</tr>
<tr>
<td>Other</td>
<td>4,743 (12.6)</td>
<td>21 (2.6)</td>
<td>87 (10.7)</td>
</tr>
<tr>
<td>Season</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>March–May</td>
<td>9,018 (23.9)</td>
<td>261 (32.2)</td>
<td>116 (14.3)</td>
</tr>
<tr>
<td>June–August</td>
<td>10,034 (26.6)</td>
<td>233 (28.8)</td>
<td>11 (1.4)</td>
</tr>
<tr>
<td>September–November</td>
<td>10,883 (28.8)</td>
<td>186 (23.0)</td>
<td>31 (3.8)</td>
</tr>
<tr>
<td>December–February</td>
<td>7,811 (20.7)</td>
<td>130 (16.1)</td>
<td>652 (80.5)</td>
</tr>
<tr>
<td>Day of week</td>
<td>0.471</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>Weekday</td>
<td>24,969 (66.2)</td>
<td>526 (64.9)</td>
<td>576 (71.1)</td>
</tr>
<tr>
<td>Weekend</td>
<td>12,777 (33.9)</td>
<td>284 (35.1)</td>
<td>234 (28.9)</td>
</tr>
<tr>
<td>Time of day</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Daytime (9:00–18:00)</td>
<td>19,920 (52.8)</td>
<td>549 (67.8)</td>
<td>473 (58.4)</td>
</tr>
<tr>
<td>Other (18:00–09:00)</td>
<td>17,826 (47.2)</td>
<td>261 (32.2)</td>
<td>337 (41.6)</td>
</tr>
</tbody>
</table>

Values are presented as number (%).

Outcomes in the farmer group, compared with the non-farmer group, are summarized in Table 4.

Injury severity (RTS and ISS) and clinical outcomes (in-hospital mortality, ICU admission, and surgery) differed significantly between the two groups in the unmatched sample. The injured patients in the farmer group had a higher injury severity, greater mortality within 14 days, and a greater rate of ICU admission, and they required surgery more frequently than those in the non-farmer group. After propensity score matching, however, the differences in injury severity and clinical outcomes were not significant between the groups, except for the indication for surgery. In the matched sample, injured patients in the farmer group had a greater rate of surgery than those in the non-farmer group.

The results of the multivariate logistic regression analysis in the unmatched sample adjusted for age, sex, inhabitant, insurance type, and year of injury, and the results of the univariate logistic regression analyses in the matched sample for the primary and secondary outcomes are summarized in Table 4. In the multivariate logistic regression analysis of the unmatched dataset (n = 38,556), farmers showed a higher likelihood of ICU admission (adjusted OR, 1.752; 95% confidence interval [CI], 1.205–2.547; P = 0.003) and higher odds of undergoing surgery overall (adjusted OR, 1.870; 95% CI, 1.569–2.229; P < 0.001), within 24 hours (adjusted OR, 3.025; 95% CI, 2.133–4.290; P < 0.001), within 48
Injury comparisons in farmers versus non-farmers

In the univariate logistic regression analyses of the propensity score–matched sample (n = 1,620), overall injury-related mortality (OR, 1.000; 95% CI, 0.321–3.114; P > 0.999), mortality ≤ 7 days (OR, 3.015; 95% CI, 0.607–14.982; P = 0.177), mortality ≤ 14 days (OR, 2.007; 95% CI, 0.500–8.054; P = 0.326), and ICU admission (OR, 1.425; 95% CI, 0.818–2.484; P = 0.211) did not differ significantly between farmers and non-farmers. However, farmers still showed higher odds of undergoing surgery overall (OR, 1.786; 95% CI, 1.377–2.317; P < 0.001), within 24 hours (OR, 2.609; 95% CI, 1.423–4.781; P = 0.002), within 48 hours (OR, 1.759; 95% CI, 1.092–2.834; P = 0.020), and within 72 hours (OR, 1.708; 95% CI, 1.109–2.629; P = 0.015) compared with non-farmers.

Table 3. Injury severity and clinical outcomes of injured patients by occupation (farmers and non-farmers)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unmatched sample (n = 38,556)</th>
<th>Matched sample (n = 1,620)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-farmer (n = 37,746)</td>
<td>Farmer (n = 810)</td>
</tr>
<tr>
<td>Revised Trauma Score</td>
<td>7.82 ± 0.29</td>
<td>7.79 ± 0.52</td>
</tr>
<tr>
<td>Injury Severity Score ≤ 8</td>
<td>2.46 ± 3.08</td>
<td>2.79 ± 3.72</td>
</tr>
<tr>
<td>9–15</td>
<td>1.51 ± 4.0</td>
<td>51 ± 6.3</td>
</tr>
<tr>
<td>≥ 16</td>
<td>247 ± 0.7</td>
<td>10 ± 1.2</td>
</tr>
<tr>
<td>Unknown</td>
<td>8,092 ± 21.4</td>
<td>132 ± 16.3</td>
</tr>
<tr>
<td>ICU admission</td>
<td>575 ± (1.5)</td>
<td>31 ± (3.8)</td>
</tr>
<tr>
<td>Surgery Overall</td>
<td>3,946 ± 10.5</td>
<td>179 ± 22.1</td>
</tr>
<tr>
<td>≤ 24 hr</td>
<td>471 ± 1.2</td>
<td>38 ± 4.7</td>
</tr>
<tr>
<td>≤ 48 hr</td>
<td>781 ± 2.1</td>
<td>48 ± 5.9</td>
</tr>
<tr>
<td>≤ 72 hr</td>
<td>1,074 ± 2.8</td>
<td>58 ± 7.2</td>
</tr>
<tr>
<td>Dead on arrival</td>
<td>24 ± (0.1)</td>
<td>2 ± (0.2)</td>
</tr>
<tr>
<td>Mortality Overall ≤ 7 day</td>
<td>1,358 ± (0.592–3.115)</td>
<td></td>
</tr>
<tr>
<td>≤ 14 day</td>
<td>2,258 ± (0.969–5.259)</td>
<td></td>
</tr>
<tr>
<td>ICU admission</td>
<td>1,792 ± (0.775–4.140)</td>
<td></td>
</tr>
<tr>
<td>Surgery Overall</td>
<td>1,752 ± (1.205–2.547)</td>
<td></td>
</tr>
<tr>
<td>≤ 24 hr</td>
<td>2,086 ± (1.578–2.757)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number (%).
ICU, intensive care unit.

Table 4. ORs for clinical outcomes in farmer versus non-farmer groups before and after matching

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unmatched sample (n = 38,556)</th>
<th>Matched sample (n = 1,620)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted OR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Mortality Overall ≤ 7 day</td>
<td>1.358 (0.592–3.115)</td>
<td>0.470</td>
</tr>
<tr>
<td>≤ 14 day</td>
<td>2,258 (0.969–5.259)</td>
<td>0.059</td>
</tr>
<tr>
<td>ICU admission</td>
<td>1,792 (0.775–4.140)</td>
<td>0.172</td>
</tr>
<tr>
<td>Surgery Overall ≤ 24 hr</td>
<td>1,870 (1.569–2.229)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>≤ 48 hr</td>
<td>2,323 (1.708–3.157)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>≤ 72 hr</td>
<td>2,086 (1.578–2.757)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Adjusted for sex, age, inhabitant, type of insurance, and year of injury.
OR, odds ratio; CI, confidence interval; ICU, intensive care unit.

DISCUSSION

We established the prospective ED-AgISS to compare the characteristics and outcomes of injuries to agricultural workers with those to nonagricultural workers. In the unmatched sample, a multivariate logistic regression analysis revealed that injury-related mortality did not differ significantly between the farmer and non-farmer groups, whereas the farmer group had higher adjusted ORs for ICU admission and surgery. After propensity
score matching, ICU admissions did not differ significantly between the farmer and non-farmer groups, but injured patients in the farmer group still required surgery more frequently than those in the non-farmer group.

Limited information is available about the clinical aspects and outcomes of nonfatal injuries to agricultural workers because obtaining comprehensive data about nonfatal injury events is more complex than obtaining data on fatal injuries [24]. Thus, the burden of injuries to agricultural workers on the ED is not well quantified.

Korea’s proportion of injuries to agricultural workers at the ED during a 4-month period was 6.3% in a pilot study for developing an ED-based occupational injury surveillance system [25]. A descriptive study in North Carolina, USA reported that an average of 459 farm injury cases occurred annually from 2008 to 2012, with little yearly variation, based on syndromic surveillance data gathered by the ED [15]. In our study of all adult patients visiting the ED, 810 injured patients were engaged in agriculture, and the overall proportion of agricultural injuries was 2.1% (range, 1.5%–3.1%) during the study period. The burden of injuries to agricultural workers reported in other studies was higher than in our study (an average of 135 cases annually and an overall proportion of 2.1%). Those differences might be due to geographic variations and the extent of the surveillance system.

Among our 810 injured agricultural workers who visited the ED, 508 (62.7%) were men, and the mean age was 61.1 ± 13.2 years. Several injury characteristics differed between the farmer and non-farmer groups in the unmatched sample. Injuries to agricultural workers (compared with nonagricultural workers) occurred mainly outdoors (90.6% vs. 57.2%), during paid work (90.0% vs. 14.4%), and involved unintentional accidents (96.2% vs. 92.2%), and the most common location was the workspace (65.4% vs. 8.6%). The major injury mechanisms were fall or slip (26.4% vs. 28.4%) and cut or penetrating injuries (20.9% vs. 12.3%), rather than motor vehicle collisions (10.3% vs. 22.5%). No one in our study population was covered by industrial insurance.

These results are consistent with previous findings that evaluated the characteristics and factors associated with agricultural injuries: a higher proportion of older individuals, more men than women, low worker compensation coverage, more accidental than intentional injuries, and major injury mechanisms involving lacerations and sprain or strain that occurred in the farm field during paid work with time variation in terms of season, days of the week, and daytime events [10,12,16,26,27].

However, most previous studies evaluated those results only in agriculturally engaged populations, whereas our study provides the detailed injury epidemiology of occupation-associated differences from nonagricultural workers. We also found that several baseline demographics of injured patients differed significantly between the farmer and non-farmer groups in the unmatched sample: sex, age, inhabitant, insurance type, distribution in the year, alcohol-relatedness, EMS usage, AVPU mental status, GCS score, systolic blood pressure <90 mmHg, and disposition (all P < 0.05). Among those factors, the five patient demographic differences (age, sex, inhabitant, insurance type, and year of injury) can be considered unique host factors prior to the injury event.

Because of concerns about the difficult-to-adjust structural confounding associated with the observational study design and the relatively small size of the farmer’s group, our analysis using a traditional regression model or covariate adjustment approach was inadequately robust in handling endogeneity bias, which made it challenging to assess the impact of occupation (farmers vs. non-farmers) on injury epidemiology and clinical outcomes. Therefore, we adopted a propensity score matching approach to balance the participants’ baseline demographics and sample size between the groups [23].

Tables 5 and 6 show the extent of the balance between the two samples before and after matching. For each matching variable, the absolute standardized mean difference was less than 0.05, indicating that the covariates were balanced in the matched samples. There was almost a 94.8% (range, 86.8%–98.5%) reduction in these covariates’ standardized mean differences after matching [22]. Fig. 2 shows the extent of covariate imbalance as standardized percentage differences using dot charts.

We also calculated overall measures of covariate imbalance before and after propensity score matching. Rubin’s B (the absolute standardized difference of the means) and Rubin’s R (the ratio of treated to nontreated variances in the propensity score index) were 7.4 and 1.28, respectively, in the matched sample, which is considered to indicate sufficient balance [23].

Only alcohol-related injury and ED disposition differed significantly among the demographics after propensity score matching; EMS usage, AVPU mental status, GCS score, and systolic blood pressure <90 mmHg did not differ significantly after matching. A possible explanation for these results is that the group demographic differences at the time of injury were associated with host factors that could not modify the characteristics of farm workers compared with non-farmers. However, one interesting finding is that the group differences in the distribution of most injury characteristics remained statistically significant in both the unmatched and matched samples. These group differences in injury characteristics, which persisted after achieving a similar dis-
Injury comparisons in farmers versus non-farmers

The distribution of host factors across farmers and non-farmers, might be associated with occupational influences.

Similar to previous studies, the results of this study show that the farmer group had significantly higher rates of ICU admission, surgery, and injury-related mortality than the non-farmer group [28–31]. However, the multivariate logistic regression analysis in the unmatched sample adjusted for age, sex, inhabitant, insurance type, and year of injury showed that the adjusted OR for injury-related mortality was not statistically significant. Furthermore, univariate logistic regression analyses of the propensity score–matched sample showed that only the OR for the rate of surgery was significant.

These findings are somewhat surprising given that other studies have reported high mortality and morbidity rates among agricultural workers [4,7,10,17,25,28–31]. A potential reason for this discrepancy could be the study design and setting. Our participants were injured patients who visited the ED. Several previous studies evaluating the mortality and morbidity of injuries to agricultural workers used data sources such as industrial compensation records, insurance claims data, and working condition surveys [12,17,25,32–34]. Therefore, the participants in our study might have had mainly nonfatal injuries because our study excluded individuals who died in the prehospital phase. Another possible reason could be our statistical analysis method. We used a multivariate logistic model and propensity score matching to control for the effect of host confounders on clinical outcomes. Therefore, our results about clinical outcomes need to be interpreted with caution and should be limited to patients with nonfatal injuries who visit an ED, rather than being extrapolated to all injuries to agricultural workers.

These findings suggest that the targets for preventing injuries to agricultural workers might differ depending on the timing of...
the injury. Primary prevention could be an important prehospital phase intervention to prevent fatal injuries to agricultural workers, such as by providing rollover protection structures and seat-belts on tractors [35]. Additionally, preventive efforts to reduce the morbidity of nonfatal injuries to agricultural workers need to be prioritized in the hospital phase. Thus, ED physicians should understand the special considerations needed to manage acute injuries to agricultural workers, including the triad of Ts: excessive time until treatment, excessive trash or wound contamination, and excessive trauma to tissues and organs [36]. Human resources sufficient to perform operations such as reconstruction, attachment, and amputation are also essential because of the high likelihood that injuries to agricultural workers will require surgery.

Our study has several limitations that require attention. First, the major limitation of our study population is that it does not adequately represent the target populations. Thus, our results must be interpreted cautiously and should not be extrapolated to the severity of all work-related agricultural injuries. Our findings represent nonfatally injured agricultural workers who visited an ED. Second, we excluded 135 participants from the 38,691 eligible participants because of missing essential variables. Although the size of the excluded sample was relatively small (0.3%), the proportion in the farmer group was significantly higher than that in the non-farmer group (2.8% vs. 0.3%, P < 0.001). Therefore, the possibility of bias other than systematic missing data cannot be excluded. Third, the regional generalizability of our study is weak because our study population was obtained from a small subset in only one province. In addition, injuries to agricultural workers have been strongly associated with environmental and safety cultures at the farm and individual levels. Therefore, the generalizability of these results to other regions might be limited.

In summary, we have identified differences in injury characteristics between agricultural and nonagricultural workers and found a significantly higher rate of surgery among agricultural workers and no significant differences in injury-related mortality in both the matched and unmatched samples. Our findings suggest the importance of tailoring injury prevention targets and strategies for agricultural workers to emphasize primary prevention for fatal injuries in the prehospital phase and preventive efforts to reduce the morbidity of nonfatal injuries in the hospital phase.

**ARTICLE INFORMATION**

**Author contributions**

Conceptualization: SWS; Data curation: HH, JB; Formal analysis: SWS, YK; Investigation: HH, JYK; Methodology: SWS, JHK; Resources: SYK, SKL; Software: SWS, WJK; Validation: WJK, JB; Visualization: SHL; Writing–original draft: JYK; Writing–review & writing: all authors. All authors read and approved the final manuscript.

**Conflicts of interest**

The authors have no conflicts of interest to declare.

**Funding**

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**Data availability**

Data analyzed in this study are available from the corresponding author upon reasonable request.

**Supplementary materials**

Supplementary Material 1. Emergency department–based agricultural injury surveillance system (ED-AgISS) expanded survey paper.

Supplementary materials are available at [https://doi.org/10.15441/ceem.23.022](https://doi.org/10.15441/ceem.23.022).

**REFERENCES**

8. The Economics Daily. Injuries, illnesses, and deaths in agricul-
9. National Institute of Agricultural Sciences of Korea. [Number of farmers, number of occupational injuries, and incidence of occupational injuries by use of agricultural machinery] [Internet]. National Institute of Agricultural Sciences of Korea; [cited 2022 Sep 28]. Available from: https://farmer.rda.go.kr/newfds/menu1/country_2_1_001.do


Characteristics of fall–from–height patients: a retrospective comparison of jumpers and fallers using a multi-institutional registry

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Objective
Fall from height (FFH) is a major public health problem that can result in severe injury, disability, and death. This study investigated how the characteristics of jumpers and fallers differ.

Methods
This was a retrospective study of FFH patients enrolled in an Emergency Department–based Injury In-depth Surveillance (EDIIS) registry between 2011 and 2018. Depending on whether the injury was intentional, FFH patients who had fallen from a height of at least 1 m were divided into two groups: jumpers and fallers. Patient characteristics, organ damage, and death were compared between the two groups, and factors that significantly affected death were identified using multivariable logistic analysis.

Results
Among 39,419 patients, 1,982 (5.0%) were jumpers. Of the jumpers, 977 (49.3%) were male, while 30,643 (81.9%) of fallers were male. The jumper group had the highest number of individuals in their 20s, with the number decreasing as age increased. In contrast, the number of individuals in the faller group rose until reaching their 50s, after which it declined. More thoracoabdominal, spinal, and brain injuries were found in jumpers. The in-hospital mortality of jumpers and fallers was 832 (42.0%) and 1,268 (3.4%), respectively. Intentionality was a predictor of in-hospital mortality, along with sex, age, and fall height, with an odds ratio of 7.895 (95% confidence interval, 6.746–9.240).

Conclusion
Jumpers and fallers have different epidemiological characteristics, and jumpers experienced a higher degree of injury and mortality than fallers. Differentiated prevention and treatment strategies are needed for jumpers and fallers to reduce mortality in FFH patients.

Keywords
Accidental falls; Wounds and injuries; Suicide; Suicide prevention

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INTRODUCTION

Fall from height (FFH) is a major cause of death and disability. The World Health Organization (WHO) reported that falls are a major public health problem worldwide as the second leading cause of injury-related death after road traffic injuries [1]. According to the Korean Statistical Information Service (KOSIS), falls account for 9.8% of injury-related deaths [2]. One study of healthcare costs for FFH patients revealed an aggregate expenditure of US$4,421,507 in 1 year, with an average cost of US$15,735 per patient. This financial burden underscores the significant impact of FFH on the healthcare financing system [3]. FFH can be divided into unintentional falls and intentional jumping. In statistics published by the Korean Ministry of Health and Welfare, in-tentional falls were the second most common method of suicide after hanging, comprising 16.5% of all cases [4]. Worldwide, suicide is the predominant cause of mortality among young individuals and has substantial socioeconomic ramifications [5]. As FFH incidents driven by suicidal intentions are rooted in mental health challenges, it is crucial to have different prevention strategies for jumpers compared to fallers. The mechanism of damage from the force generated by rapid vertical deceleration and direct collision with the ground or an object applies equally to people who have fallen unintentionally or those who have jumped, but the clinical characteristics and patterns of damage differ [6–10]. Due to the high mortality rate of FFH, several autopsy-based studies have been published [11–13]. Studies reporting the clinical characteristics of FFH patients in the medical field have focused primarily on accidental falls, as this accounts for the majority of FFH cases [3,14–16]. Some studies have also compared jumpers and fallers; however, these studies are not representative because they included only a small number of jumpers [6,10,17,18].

In this study, we aimed to compare the characteristics of jumpers and fallers using a multi-institutional registry and to determine factors that affect the prognosis of FFH patients in the emergency department (ED).

METHODS

Ethics statement

This study was approved by the Institutional Review Board of Severance Hospital (No. 4–2019-0692). The requirement for informed consent was waived due to the retrospective nature of the study. All data were completely anonymous.

Study design and data source

This retrospective, observational, cohort study used data from the Emergency Department-based Injury In-depth Surveillance (EDIIS) registry between 2011 and 2018) of the Korea Disease Control and Prevention Agency (KDCA). Twenty-three institutions participated in this surveillance survey. Trained researchers from each institution collected the clinical information of injured patients who presented to the ED. KDCA provided continuous education programs for researchers to manage the quality of the data, performed a qualitative assessment of each institution’s data, and provided periodic feedback.

Study population and data collection

Our study included patients aged 10 years or older who fell from a height of 1 m or more. Patients were divided into two groups according to intention: jumpers and fallers. Patients who injured themselves unintentionally were categorized as fallers, while those who were injured due to self-harm or suicide attempts were designated as jumpers. Incidents involving homicide, violence, or intentions that remained unknown were excluded from this study.

The following variables were reviewed in the current study: sex, age, height of fall, type of insurance, mode of ED arrival, date and time of ED arrival, place where the injury occurred, alcohol drink-
ing, ED treatment results, in-hospital mortality, and trauma-related diagnoses. Patients were divided into 10-year age groups to determine incidence according to age. Fall height was classified as 1 to 4 m and ≥ 4 m. Insurance types were categorized as National Health Insurance, Medicaid, and other. Seasons were defined based on the arrival date at the ED as follows: spring (March–May), summer (June–August), autumn (September–November), and winter (December–February). The mode of ED arrival was divided into emergency medical service (EMS), private ambulance, and other. The place where injuries occurred was classified as factory, residential area, nature, public or commercial area, road, farm, sports facility, school, hospital, or other. Alcohol consumption was assessed through history taking or blood ethanol level analysis and categorized as yes, no, or unknown. Death on arrival and expiration in the ED were considered in-hospital mortality. Diagnoses were reported in accordance with the International Classification of Diseases, 10th Revision (ICD-10). We investigated the patient’s primary diagnosis and 2nd to 10th diagnoses and identified the injured organs using the following codes: epidural hemorrhage (S06.4), subdural hemorrhage (S06.5), subarachnoid hemorrhage (S06.6), intracranial hemorrhage (S06.8), pneumothorax (S27.0, S27.2), hemothorax (S27.1, S27.2), flail chest (S22.5), liver injury (S36.1), spleen injury (S36.0), kidney injury (S37.0), hollow viscous organ injury (S36.3, S36.4, S36.5, S36.6), aorta injury (S25.0, S35.0), cervical spine fracture (S12.0, S12.1, S12.2, S12.7), thoracic spine fracture (S22.0, S22.1), lumbar spine and pelvis fracture (S32), upper extremity fracture (S42, S52, S62), and lower extremity fracture (S72, S82, S92).

Statistical analysis
We compared the demographic characteristics, treatment outcomes, and injured organs between the jumper and faller groups. Categorical variables are presented as numbers and percentages, and continuous variables are presented as means and standard deviations. The chi-square test or Fisher exact probability test and independent sample t-test were used for analysis. Multivariable logistic regression analysis was performed to identify factors that influenced in-hospital mortality. Variables with significant differences between the death and survival groups (P < 0.1) were selected as confounding variables. Statistical analyses were conducted using SAS ver. 9.4 (SAS Inc). Statistical significance was set at a two-tailed P < 0.05.

RESULTS
Among the 2,143,189 patients registered in the EDIIS registry from 2011 to 2018, 645,308 (30.1%) presented to the ED due to a fall (Fig. 1). After excluding 584,562 patients who had fallen from less than 1 m in height and 3,433 patients whose fall height was unknown, 57,313 patients were determined to have FFH. Of these, 39,419 patients were included in the study after excluding 17,192 patients under the age of 10 years and 702 patients with unknown intent. The numbers of jumpers and fallers were 1,982 (5.0%) and 37,437 (95.0%), respectively.

General characteristics
Of the jumpers, 977 (49.3%) were male, while 30,643 fallers (81.9%) were male (Table 1). The mean ± standard deviation age of the jumper group was 38.7 ± 19.5 years, which was younger than the faller group (48.5 ± 17.8 years, P < 0.001). In the jumper group, 1,663 (83.9%) had fallen from a height of 4 m or more, whereas only 7,148 (19.1%) of those in the faller group had fallen from such a height (P < 0.001). The frequency of EMS use was 1,445 (72.9%) in jumpers and 14,779 (39.5%) in fallers (P < 0.001). In the jumper group, the place of fall occurrence was predominantly in the residential area (n = 1,587, 80.1%), while most FFH occurred in the factory setting (n = 12,401, 33.1%) in the faller group. Alcohol consumption was higher in the jumper group than in the faller group (399 [20.1%] vs. 2,926 [7.8%], P < 0.001). Unknown alcohol levels were also higher in the jumper
Differences between jumpers and fallers

Age and time distribution
The age distribution of each group was analyzed according to sex (Fig. 2). In the jumper group, the largest number of individuals was in their 20s, with the prevalence decreasing by age. There was no meaningful difference in distribution according to sex in the jumper group. In fallers, the incidence of females was evenly distributed across all age groups, whereas the incidence of falls increased in men until their 50s and then decreased. Fig. 3 shows the distribution of visits per hour. Jumpers presented to the ED most frequently between 0:00 and 2:00 AM and in a relatively uniform manner in the remaining hours of the day, whereas fallers were more likely to present between 10:00 AM and 7:00 PM.

Injured organs
A comparison of injured organs between the two groups is presented in Table 2. The incidence of severe head injuries, such as epidural and subdural hemorrhages, was higher in fallers. The incidence of subarachnoid and intracranial hemorrhages did not differ between the two groups. Chest injuries such as pneumothorax, hemothorax, and flail chest occurred more frequently in the jumper group. Intra-abdominal organs (liver, spleen, and kidneys) were more likely to be injured in the jumper group than in fallers.

Table 1. Comparison of patient characteristics between the jumpers and fallers

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n= 39,419)</th>
<th>Jumper (n= 1,982)</th>
<th>Faller (n= 37,437)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Male</td>
<td>31,620 (80.2)</td>
<td>977 (49.3)</td>
<td>30,643 (81.9)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>7,799 (19.8)</td>
<td>1,005 (50.7)</td>
<td>6,794 (18.1)</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>48.0 ± 18.0</td>
<td>38.7 ± 19.5</td>
<td>48.5 ± 17.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Height of fall (m)</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>1–4</td>
<td>30,608 (77.6)</td>
<td>319 (16.1)</td>
<td>30,289 (80.9)</td>
<td></td>
</tr>
<tr>
<td>&gt; 4</td>
<td>8,811 (22.4)</td>
<td>1,663 (83.9)</td>
<td>7,148 (19.1)</td>
<td></td>
</tr>
<tr>
<td>Type of insurance</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>National Health Insurance</td>
<td>32,343 (82.0)</td>
<td>1,476 (74.5)</td>
<td>30,867 (82.5)</td>
<td></td>
</tr>
<tr>
<td>Medicaid</td>
<td>1,240 (3.1)</td>
<td>171 (8.6)</td>
<td>1,069 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5,836 (14.8)</td>
<td>335 (16.9)</td>
<td>5,501 (14.7)</td>
<td></td>
</tr>
<tr>
<td>Mode of arrival</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Emergency medical service</td>
<td>16,224 (41.2)</td>
<td>1,445 (72.9)</td>
<td>14,779 (39.5)</td>
<td></td>
</tr>
<tr>
<td>Private ambulance</td>
<td>9,341 (23.7)</td>
<td>463 (23.4)</td>
<td>8,878 (23.7)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>13,854 (35.1)</td>
<td>74 (3.7)</td>
<td>13,780 (36.8)</td>
<td></td>
</tr>
<tr>
<td>Season</td>
<td></td>
<td></td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>Spring (March–May)</td>
<td>10,116 (25.7)</td>
<td>515 (26.0)</td>
<td>9,601 (25.6)</td>
<td></td>
</tr>
<tr>
<td>Summer (June–August)</td>
<td>10,807 (27.4)</td>
<td>560 (28.3)</td>
<td>10,247 (27.4)</td>
<td></td>
</tr>
<tr>
<td>Autumn (September–November)</td>
<td>11,534 (29.3)</td>
<td>514 (25.9)</td>
<td>11,020 (29.4)</td>
<td></td>
</tr>
<tr>
<td>Winter (December–February)</td>
<td>6,962 (17.7)</td>
<td>393 (19.8)</td>
<td>6,569 (17.5)</td>
<td></td>
</tr>
<tr>
<td>Place</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Factory</td>
<td>12,405 (31.5)</td>
<td>4 (0.2)</td>
<td>12,401 (33.1)</td>
<td></td>
</tr>
<tr>
<td>Residential area</td>
<td>9,586 (24.3)</td>
<td>1,587 (80.1)</td>
<td>7,999 (21.4)</td>
<td></td>
</tr>
<tr>
<td>Nature</td>
<td>4,501 (11.4)</td>
<td>62 (3.1)</td>
<td>4,439 (11.9)</td>
<td></td>
</tr>
<tr>
<td>Public or commercial area</td>
<td>4,498 (11.4)</td>
<td>124 (6.3)</td>
<td>4,374 (11.7)</td>
<td></td>
</tr>
<tr>
<td>Road</td>
<td>3,362 (8.5)</td>
<td>111 (5.6)</td>
<td>3,251 (8.7)</td>
<td></td>
</tr>
<tr>
<td>Farm</td>
<td>2,001 (5.1)</td>
<td>0 (0)</td>
<td>2,001 (5.3)</td>
<td></td>
</tr>
<tr>
<td>Sports facility</td>
<td>1,011 (2.6)</td>
<td>0 (0)</td>
<td>1,011 (2.7)</td>
<td></td>
</tr>
<tr>
<td>School</td>
<td>990 (2.5)</td>
<td>27 (1.4)</td>
<td>963 (2.6)</td>
<td></td>
</tr>
<tr>
<td>Hospital</td>
<td>365 (0.9)</td>
<td>54 (2.7)</td>
<td>311 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>700 (1.8)</td>
<td>13 (0.7)</td>
<td>687 (1.8)</td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>3,325 (8.4)</td>
<td>399 (20.1)</td>
<td>2,926 (7.8)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>33,643 (85.3)</td>
<td>1,256 (63.4)</td>
<td>32,387 (86.5)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>2,451 (6.2)</td>
<td>327 (16.5)</td>
<td>2,124 (5.7)</td>
<td></td>
</tr>
<tr>
<td>Hospital admission</td>
<td>19,268 (48.9)</td>
<td>932 (47.0)</td>
<td>18,336 (49.0)</td>
<td>0.009</td>
</tr>
<tr>
<td>Intensive care unit admission</td>
<td>6,413 (16.3)</td>
<td>632 (31.9)</td>
<td>5,781 (15.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Int-hospital mortality</td>
<td>2,100 (5.3)</td>
<td>832 (42.0)</td>
<td>1,268 (3.4)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Values are presented as number (%) or mean±standard deviation.
the faller group. The incidence of aorta and spine injuries was significantly higher in the jumper group. Upper extremity injuries were more frequent in fallers, but lower extremity injuries were more common in jumpers (524 [26.4%] vs. 6,117 [16.3%], $P < 0.001$).

**Prognostic factors of in-hospital mortality**

Table 3 shows the results of the multivariable regression analysis used to identify factors that affect in-hospital mortality in FFH patients. The female to male odds ratio for in-hospital mortality was low, at 0.775 (95% confidence interval [CI], 0.679–0.885; $P < 0.001$). Age was determined to be a factor, with the mortality rate increasing with age. Fall height and intentionality were significantly associated with in-hospital mortality with an odds ratio of 4.808 (95% CI, 4.286–5.394) and 7.895 (95% CI, 6.746–9.240), respectively.

**DISCUSSION**

Trauma due to FFH is a major challenge for society because it results in multiple severe injuries, permanent disability, and high
Table 2. Comparison of injured organs between the jumpers and fallers

<table>
<thead>
<tr>
<th>Injured organ</th>
<th>Jumper (n=1,982)</th>
<th>Faller (n=37,437)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Head</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subdural hemorrhage</td>
<td>78 (3.9)</td>
<td>2,537 (6.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>69 (3.5)</td>
<td>1,391 (3.7)</td>
<td>0.591</td>
</tr>
<tr>
<td>Epidural hemorrhage</td>
<td>33 (1.7)</td>
<td>1,117 (3.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>23 (1.2)</td>
<td>480 (1.3)</td>
<td>0.638</td>
</tr>
<tr>
<td><strong>Chest</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>277 (14.0)</td>
<td>1,429 (3.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemothorax</td>
<td>240 (12.1)</td>
<td>1,655 (4.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Flail chest</td>
<td>11 (0.6)</td>
<td>65 (0.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Abdomen</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver injury</td>
<td>88 (4.4)</td>
<td>393 (1.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spleen injury</td>
<td>28 (1.4)</td>
<td>227 (0.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Kidney injury</td>
<td>25 (1.3)</td>
<td>203 (0.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hollow viscus organ injury</td>
<td>3 (0.2)</td>
<td>48 (0.1)</td>
<td>0.743</td>
</tr>
<tr>
<td><strong>Aorta</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical spine fracture</td>
<td>67 (3.4)</td>
<td>857 (2.3)</td>
<td>0.002</td>
</tr>
<tr>
<td>Thoracic spine fracture</td>
<td>136 (6.9)</td>
<td>1,855 (5.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lumbar spine and pelvis fracture</td>
<td>699 (35.3)</td>
<td>5,927 (15.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Extremity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper extremity fracture</td>
<td>266 (13.4)</td>
<td>5,789 (15.5)</td>
<td>0.014</td>
</tr>
<tr>
<td>Lower extremity fracture</td>
<td>524 (26.4)</td>
<td>6,117 (16.3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are presented as number (%).

mortality. Understanding the clinical characteristics and injury patterns of FFH patients can help in the emergency treatment of these patients, and their epidemiological characteristics are valuable basic data for establishing prevention strategies. This study is meaningful because it presents representative clinical features of jumpers based on analyses of a relatively large number of patients from a multi-institutional registry. From an epidemiological perspective, jumpers and fallers had different sex and age distributions. There was also a significant difference in the severity of injury and mortality between the two groups.

According to the Korean White Paper on Suicide Prevention [4], published in 2022, the most common means of suicide after hanging are falling and gas poisoning. There are differences in the preferred means of suicide according to age group. In 2022, 35.7% of adolescent suicide patients died from falls, while 17.4% of elderly patients died from falls. This study also confirmed that the frequency of jumping was high among young people and rapidly decreased with age in both sexes. Whether a fall victim has attempted suicide may not be immediately ascertainable when they first present at the ED. The results of this study suggest that serious injuries and suicide attempts should be suspected in young FFH patients. In addition, considering differences in the means used to attempt suicide by age, more effective policies for suicide prevention can be established. In particular, when implementing a suicide prevention project for falls, targeting the younger generation will lead to more effective suicide reduction [19].

Patients who had fallen unintentionally were predominantly male, and the distribution by age was highest among those in their 50s. Most accidents tended to occur in factories during the daytime, suggesting that most falls occurred while working at heights. Globally, FFH is the leading cause of fatal injuries in construction workers [20]. Along with an aging society, the average age of construction workers is also increasing [21,22]. According to the US Bureau of Labor Statistics, the average age of construction workers in 2022 was 42.5 years [23]. The average age in Korea is higher than this; according to an investigation by the Korean Ministry of Employment and Labor, it was 53.1 years old in 2022 [24]. Older construction workers are generally more prone to work-related injuries. Indeed, physical decline, reduced coordination, and slow reaction times can increase the chances of accidents, musculoskeletal injuries, and falls in older construction workers [22]. Safety education, use of protective equipment, and compliance with safety guidelines should be conducted considering the increasing age of construction workers [25,26].

More thoracoabdominal organ and spinal injuries occurred in jumpers than in fallers. This is consistent with existing studies in that jumpers typically fall from greater heights and exhibit higher severity and mortality rates [27,28]. However, brain injuries were more frequent in patients who accidentally fell than in jumpers. While this outcome might appear surprising, other studies have
similarly reported fewer head injuries among jumpers [29,30]. This should be interpreted with caution because we studied only those patients who were transferred to the hospital. It has been noted in previous studies that patients who land on their heads tend not to arrive at the hospital alive [31,32]. Another notable injury pattern was that jumpers displayed a higher incidence of lower extremity fractures than fallers. This finding aligns with those of previous studies that compared skeletal injuries between jumpers and fallers, emphasizing that jumpers frequently first contact the landing surface with their feet [6,7,27].

We confirmed that fall height, age, and suicidal intent were major determinants of death. This is consistent with the results of previous studies on the determinants of death in fall patients [33,34]. Fall height is a major factor that influences vertical deceleration injury patterns, with studies suggesting 6 or 7.5 m as the height of a fatal fall [35–38]. Jumpers tended to fall from a greater height than fallers, but even after adjusting for fall height, suicide intent remained a significant factor in mortality.
Our registry only investigated fall height based on a height of 4 m; therefore, the effect of height on death may not have been adequately examined. However, previous studies have suggested that suicide attempts are a significant independent factor of death in fall patients [18,33]. This suggests that the difference in the risk of death between jumpers and fallers could be due not only to the height of the fall, but also to other factors such as use of protective gear or alcohol or drugs. Furthermore, a study conducted by Faggiani et al. [39] revealed that 76.9% of jumpers had received a diagnosis of a psychiatric disorder (mainly major depressive disorder and bipolar disorder) prior to the incident, and psychiatric illness played a role in extended hospitalization and prolonged stays in the intensive care unit. These underlying psychiatric conditions, coupled with the socioeconomic disadvantages experienced by jumpers, are influential factors that could potentially increase mortality rates. These elements must be considered when devising suicide prevention initiatives related to FFH.

This study has several limitations. First, patients with unknown intentions were excluded. The exclusion of severely ill patients whose intent could not be ascertained because they were unconscious or dead may have influenced the results. Second, patients who could not undergo diagnostic imaging due to an unstable condition or death at the time of arrival at the ED were omitted from the analyses of organ and spinal injuries.

In conclusion, jumpers and fallers had distinct epidemiological characteristics, with jumpers having a higher degree of injury and mortality than fallers. Understanding the characteristics of FFH patients by dividing them into jumpers and fallers could serve as a basis for effective preventive and clinical actions and optimizing hospital treatment.

ARTICLE INFORMATION

Author contributions
Conceptualization: all authors; Data curation: MJK; Formal analysis: JYH, MJK; Funding acquisition: MJK, JHL; Visualization: JYH, MJK; Writing–original draft: JJ, JYH, MJK; Writing–review & editing: all authors. All authors read and approved the final version of the manuscript.

Conflicts of interest
The authors have no conflicts of interest to declare.

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Data availability
Data analyzed in this study are available from the corresponding author upon reasonable request.

REFERENCES


Trends in emergency department visits for emergency care–sensitive conditions before and during the COVID–19 pandemic: a nationwide study in Korea, 2019–2021

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Objective Emergency care systems worldwide have been significantly affected by the COVID–19 pandemic. This study investigated the trend of emergency department (ED) visits for emergency care–sensitive conditions (ECSCs) in Korea before and during the pandemic.

Methods We performed a longitudinal study using the national ED database in Korea from January 2019 to December 2021. We calculated the number and incidence rate of visits for ECSCs per 100,000 ED visits, and the incidence rate ratio of 2021 relative to the value in 2019. The selected ECSCs were intracranial injury, ischemic heart disease, stroke, and cardiac arrest.

Results The number of ED visits for all causes decreased by about 23% during the pandemic. The number of ED visits for intracranial injuries decreased from 166,695 in 2019 to 133,226 in 2020 and then increased to 145,165 in 2021. The number of ED visits for ischemic heart disease and stroke decreased in 2020 but increased to 2019 levels in 2021. In contrast, the number of ED visits for cardiac arrest increased from 23,903 in 2019 to 24,344 in 2020 and to 27,027 in 2021. The incidence rate and incidence rate ratio of these four ECSCs increased from 2019 to 2021, suggesting increasing relative proportions of ECSCs in total ED visits.

Conclusion During the COVID–19 pandemic, the number of cardiac arrests seen in the EDs increased, but that of other ECSCs decreased. The decrease in ED visits for ECSCs was not as pronounced as the decrease in ED visits for all causes during the pandemic. Further studies are needed to determine clinical outcomes in patients with ECSC during the pandemic.

Keywords COVID–19; Pandemics; Emergency departments

INTRODUCTION

After the first case of COVID–19 was reported in Wuhan, China, in December 2019, this dangerous epidemic spread worldwide [1]. By July 2023, the World Health Organization (WHO) reported that more than 760 million people were infected with COVID–19, and more than 6.9 million of those infected had died [2]. In regions critically impacted by COVID–19 cases, such as Europe
What is already known
Emergency care systems worldwide have been severely impacted by the COVID-19 pandemic.

What is new in the current study
During the COVID-19 pandemic period, the number of emergency department visits for all causes and emergency care–sensitive conditions, including intracranial injury, ischemic heart disease, and stroke, has decreased significantly in Korea. On the other hand, the number of cardiac arrests has increased.

and North America [3], substantial medical resources were required to respond to this situation [4]. Moreover, these efforts had to be carried out while ensuring continued access to essential health care services [5]. However, emerging studies have suggested that the COVID-19 pandemic had a negative impact on health care utilization [6]. A study conducted in five states in the United States [7] found that emergency department (ED) visits decreased by 41.5% to 63.5% in the 4 months following the pandemic outbreak compared to before the pandemic. Another Canadian study [8] found that the decline in ED visits continued for more than two years after the start of the pandemic. These declines in access to EDs are raising concerns that patients with acute life-threatening conditions such as acute myocardial infarction (AMI), stroke, and out-of-hospital cardiac arrest (OHCA) may not be able to access prompt care. In fact, there was a 10% decrease in AMI patients who visited the ED for coronary artery revascularization during the first wave of the COVID-19 pandemic in Korea [9].

Despite growing concerns, the impact of the pandemic on the emergency care system has not been fully studied. Most studies are limited to the first year of the pandemic, and nationwide data are limited. Considering that the pandemic has put a strain on the emergency care system over the past 2 years, longer-term studies are needed. Therefore, this study aims to explore the changes in ED visits for emergency care–sensitive conditions (ECSCs) in Korea before and during the pandemic using national data.

METHODS

Ethics statement
This study was approved by the Institutional Review Board of the National Medical Center (No. NMC-2021-10-123). The requirement for informed consent was waived due to the retrospective nature of the study.

Data source
This was a retrospective time-series study using data from the National Emergency Department Information System (NEDIS) between 2019 and 2021. NEDIS is a nationwide information system developed in 2003 to collect and store information on patients visiting EDs in Korea. The NEDIS database is designed to assist professionals and policy makers involved in emergency care at the regional and national levels to evaluate the performance of the emergency care system and to support future strategic planning. To this end, NEDIS provides a framework for collecting, storing, and sharing standardized data. Through NEDIS, participating EDs transmit visit-level patient data, including demographic, administrative, and clinical information, to a central processing facility. All patient-related information is anonymized and transmitted electronically, and data inconsistencies are detected manually and using computational algorithms. Detailed design and variables of the NEDIS database have been described elsewhere [9–12].

Study population
From the NEDIS database, we identified all ED patients and those with ECSCs as the primary diagnosis between January 1, 2019, and December 31, 2021. According to the definition of ECSC, we selected four of 50 time-sensitive condition candidates presented in previous studies using a multidisciplinary expert consensus method [13,14], considering the incidence and disease burden in Korea. The four ECSCs selected for the study were ischemic heart disease (IHD), stroke, cardiac arrest, and intracranial injury. The International Classification of Diseases, 10th Revision (ICD-10) codes for ECSCs are presented in Supplementary Table 1.

Outcomes
The primary outcome of interest was the number and incidence rate (IR) of ED visits for ECSCs during the study period. The sec-
ondary outcome was the incidence rate ratio (IRR) of ED visits for ECSCs.

**Statistical analysis**

The number and IRs of ED visits for ECSCs were calculated for each ECSC by calendar month. ED visit trends for ECSCs were presented as line charts according to calendar months from 2019 to 2021. The IR of ECSC per 100,000 ED visits was defined as follows:

\[
IR = \frac{\text{Monthly no. of ED visits for ECSC}}{\text{Monthly no. of total ED visits}} \times 10^5
\]

To estimate changes in ED visits for ECSCs before and during the pandemic, 2019 was designated as the before pandemic period, while 2020 and 2021 were designated as the during pandemic period. Poisson regression was used to calculate IRR and 95% confidence intervals, which are IR comparisons for ECSCs before and during the pandemic.

The database construction and statistical analysis were performed using SAS ver. 9.4 (SAS Institute) and R ver. 4.1.1. (R Foundation for Statistical Computing). Results with a two-tailed \(P < 0.05\) were considered statistically significant.

**RESULTS**

Between 2019 and 2021, the participation rate of nationwide EDs in the NEDIS was 99.8% (401 of 402) in 2019, 100% (403 of 403) in 2020, and 100% (405 of 405) in 2021. From the NEDIS, we identified a total of 23,840,990 ED visits from January 1, 2019, to December 31, 2021. Of these, 9,311,768 patients visited EDs before the pandemic period, and 14,529,222 patients visited EDs during the pandemic period (Table 1). The number of ED visits for all causes during the pandemic period decreased by about 23% compared to the pre-pandemic period. However, the number of ED visits for ECSCs showed a smaller decrease or even increased. The number of ED visits for intracranial injuries decreased by about 20% in 2020 and by 13% in 2021 compared to before the pandemic period. The number of ED visits for IHD and stroke decreased in 2020 but increased to 2019 levels in 2021. In contrast, the number of ED visits for cardiac arrest continued to increase during the pandemic.

The IRRs of ED visits for ECSCs are presented in Table 3. The IRR of ED visits for intracranial injury was 1.04 (95% CI, 1.03–

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**Table 1.** Number of emergency department visits for ECSC, 2019–2021

<table>
<thead>
<tr>
<th>ECSC</th>
<th>2019(^a) (n = 9,311,768)</th>
<th>2020(^b) (n = 7,153,969)</th>
<th>2021(^b) (n = 7,375,253)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial injury</td>
<td>166,695 (1.8)</td>
<td>133,226 (1.9)</td>
<td>145,165 (2.0)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>27,618 (0.3)</td>
<td>24,725 (0.3)</td>
<td>25,588 (0.3)</td>
</tr>
<tr>
<td>Stroke</td>
<td>102,496 (1.1)</td>
<td>94,684 (1.3)</td>
<td>99,095 (1.3)</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>23,903 (0.3)</td>
<td>24,344 (0.3)</td>
<td>27,027 (0.4)</td>
</tr>
</tbody>
</table>

Values are presented as number (%).

ECSC, emergency care–sensitive condition.

\(^a\)Before the COVID-19 pandemic. \(^b\)During the COVID-19 pandemic.

**Table 2.** IRRs of emergency department visits for ECSCs, 2019–2021

<table>
<thead>
<tr>
<th>ECSC</th>
<th>2019(^a)</th>
<th>2020(^b)</th>
<th>2021(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial injury</td>
<td>1,790.2</td>
<td>1,862.3</td>
<td>1,968.3</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>296.6</td>
<td>345.6</td>
<td>346.7</td>
</tr>
<tr>
<td>Stroke</td>
<td>1,100.7</td>
<td>1,323.5</td>
<td>1,343.6</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>256.7</td>
<td>340.3</td>
<td>366.5</td>
</tr>
</tbody>
</table>

IR, incidence rate; ECSC, emergency care–sensitive condition; CI, confidence interval.

\(^a\)Before the COVID-19 pandemic. \(^b\)During the COVID-19 pandemic.
In this study, we found that the number of overall ED visits in Korea decreased sharply during the COVID-19 pandemic. However, the decrease was less pronounced for ECSCs. In fact, the number of ED visits for cardiac arrest increased. The IRR of ED visits for ECSCs increased during the pandemic, and the IRR of ED visits for ECSCs in 2021 was significantly higher than that in 2020. This suggests that the decrease in ED visits for ECSCs was not as pronounced as the decrease in ED visits for all causes during the pandemic period. This may be because individuals with ECSCs were more likely to seek care at the ED during the pandemic due to the increased risk of complications from their condition. Additionally, the increase in ED visits for cardiac arrest during the pandemic could be due to the worsening condition of patients with originally acute conditions due to delay in seeking emergency care [15].

The decrease in ED visits may reflect a decrease in the actual need for emergency care, a decrease in access to emergency care, or a combination of both. Several factors may have contributed to the decrease in ED visits for ECSCs during the pandemic period, including social distancing, public fear of COVID-19, and diversion of patients to COVID-19-designated hospitals. For some types of ECSCs, the decrease in ED visits may be due to a “true” decrease in the number of cases. Korea, like other countries, has implemented nonpharmaceutical interventions (NPIs) such as telecommuting, travel restrictions, and gathering bans to reduce the transmission of COVID-19 through person-to-person contact [16]. These NPIs, known as social distancing, led to a significant decrease in outdoor activities and public transportation use, which can explain the decrease in ED visits due to injuries [17,18]. In our study, we found that the number of ED visits for intracranial injuries decreased the most among ECSCs. This finding is consistent with previous studies that have shown a decrease in the incidence of traumatic brain injury following the outbreak of the pandemic [19–22]. For other types of ECSCs, the decrease in ED visits may be due to fear of infection and subsequent avoidance of hospitals [23,24]. For example, individuals may not have sought emergency care because of the fear of exposure to COVID-19 in crowded emergency rooms and the concern about the possibility of extended waiting times [25]. Finally, the Korean government has designated and operated several hospitals only for patients with COVID-19 [26]. However, these measures can increase the challenge for patients with non–COVID-19 emergency conditions in accessing emergency care.

The decrease in the number of ED visits suggests that a significant number of people postponed or canceled ED visits even though they were experiencing acute conditions. ECSC essentially consists of time-sensitive conditions. According to a previous study conducted in Korea [14], delays in hospital access time in ECSCs were associated with increased mortality. Therefore, it is necessary to study whether their long-term clinical outcomes are worse. The decrease in ED visits for ECSCs is concerning as it may lead to worse long-term outcomes for patients with these conditions. It is important to understand the reasons for the decrease in ED visits for ECSCs to develop strategies for mitigating the impact of the pandemic on these patients.

This study has several notable limitations. First, it compared ED visits during the pandemic to those in the year before the pandemic. Long-term changes in the pre-pandemic period were not included in the study. Second, the definition of ECSCs is based solely on ICD-10 codes. Therefore, there is a possibility of misclassification. Third, study populations were not assessed for severity. This means that it is not possible to know the severity of patient conditions, which could impact the results of the study. For example, patients with more urgent conditions may be more likely to seek care at the ED, even during a pandemic. Finally, the study did not assess the clinical outcomes of patients with ECSCs who delayed or canceled ED visits during the pandemic. Further research is needed on this topic.

In conclusion, during the COVID-19 pandemic, the total ED visits for all causes decreased, but the IRs of the ECSCs increased. The number of cardiac arrests increased, but other ECSCs including IHD, stroke, and intracranial injuries, decreased. Understanding the specific conditions that led to the biggest decrease in ED visits during the pandemic is important in planning for the next

| Table 3. IRRs of emergency department visits for ECSCs, 2019–2021 |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                | IRR  | 95% CI          | IRR  | 95% CI          |
| Intracranial injury     | 1.04 | 1.03–1.05       | 1.10 | 1.09–1.11       |
| Ischemic heart disease  | 1.17 | 1.15–1.19       | 1.17 | 1.15–1.19       |
| Stroke                  | 1.20 | 1.19–1.21       | 1.22 | 1.21–1.23       |
| Cardiac arrest          | 1.33 | 1.30–1.35       | 1.43 | 1.40–1.45       |

IRRs for each year during the COVID-19 pandemic is calculated relative to 2019 (before the COVID-19 pandemic).

IRR, incidence rate ratio; ECSC, emergency care–sensitive condition; CI, confidence interval.
pandemic, regarding potential vulnerabilities in the emergency care system.

ARTICLE INFORMATION

Author contributions
Conceptualization: SK, EK, SJK; Data curation: SK, JL; Formal analysis: SK, HKS; Funding acquisition: HKS; Methodology: HKS; Writing—original draft: SK, HKS; Writing—review & editing: all authors. All authors read and approved the final manuscript.

Conflicts of interest
The authors have no conflicts of interest to declare.

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The authors acknowledge the late Dr. Han-duk Yoon for his dedication in establishing the National Emergency Department Information System (NEDIS).

Supplementary materials
Supplementary Table 1. The ICD-10 codes for the selected ECSCs
Supplementary materials are available from https://doi.org/10.15441/ceem.23.087.

REFERENCES


Tranexamic acid for angiotensin-converting enzyme inhibitor–induced angioedema

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Approximately 0.7% of patients taking angiotensin-converting enzyme inhibitors (ACEIs) develop ACEI-induced angioedema (ACEI-IA). With no approved treatments for ACEI-IA, the risk of complications is concerning. Tranexamic acid (TXA) has the potential to prevent intubations and resolve ACEI-IA by inhibiting the downstream production of bradykinin. In this review, we aim to evaluate the safety and efficacy of TXA use in ACEI-IA. We queried the PubMed database for studies involving TXA for ACEI-IA from January 2003 to January 2023. Seven studies met the study inclusion criteria. Our results demonstrate that TXA may improve angioedema symptoms and prevent intubation. In addition, its availability, low cost, and safety profile support its use for improving the symptoms and complications of ACEI-IA in an emergency setting.

Keywords Angiotensin-converting enzyme inhibitor–induced angioedema; Bradykinin-mediated angioedema; Tranexamic acid; Angiotensin-converting enzyme inhibitors; Drug-induced angioedema

INTRODUCTION

Approximately 30% to 40% of all angioedema-related emergencies are caused by angiotensin-converting enzyme inhibitor (ACEI) medications [1]. The populations with the highest risk of developing ACEI-induced angioedema (ACEI-IA) are women and African Americans, who are nearly 4.5 times more likely to develop ACEI-IA [2,3].

ACEI-IA, a potentially fatal complication of ACE inhibition, occurs in up to 0.7% of patients treated with ACEIs. The incidence of ACEI-IA is the highest within the first month of therapy, ac-
counting for nearly one-third of all cases [4]. However, the onset of ACEI-IA can occur any time after initiation and has been reported as late as 20 years after treatment commences [5]. Lisinopril is the most common causative agent in 87.2% of reported ACEI-IA cases, with lower rates reported in other ACEIs such as enalapril 4.3% and benazepril 3.0% [3,6].

**CLINICAL MANIFESTATIONS AND CURRENT TREATMENT**

The pathophysiology of angioedema involves a rapid increase in vascular permeability and subsequent submucosal edema. With ACE inhibition, the reduced kininase II mediated degradation of substance P and bradykinin causes excessive vasodilation and plasma extravasation [4,7].

An attack of ACEI-IA typically lasts 48 to 72 hours, and patients require hospital admission in most cases [7,8]. Nearly 10% of all ACEI-IA cases require intubation within the first 6 hours of symptom onset [9]. In addition, approximately 40% of ACEI-IA patients are admitted to the intensive care unit for an average length of 2.2 days [9,10]. First-line treatment for ACEI-IA is an immediate cessation of ACEI and active airway management.

Given the prevalent use of ACEIs, there is an urgent clinical need for a rapidly effective therapeutic intervention for severe ACEI-IA. The successful use of tranexamic acid (TXA) for the prophylaxis of acquired angioedema was first reported in an emergency setting by Beauchene et al. [11] in 2018. This review aims to investigate the efficacy of TXA use in the acute management of ACEI-IA.

**LITERATURE REVIEW**

We searched the literature for TXA and ACEI-IA in the PubMed database with the following search terms: “tranexamic acid for bradykinin angioedema” and “tranexamic acid for angiotensin-converting enzyme inhibitor-induced angioedema.” The results were limited to observational studies, case reports, case series, and literature reviews published within the last 20 years and resulted in 54 eligible studies. After excluding studies evaluating tranexamic use in hereditary angioedema or non–bradykinin-mediated angioedema, there were seven articles for full-text review.

Included parameters of interest were study name, study type, sample size, primary outcomes, and results. The key findings of the search results are listed in Table 1 [11–17]. Key primary endpoints of interest included the percentage of patients with resolved or improved angioedema, overall intubation rates, and treatment–related adverse effects. For treatment maintenance studies, the frequency of acute angioedema attacks, treatment efficacy, and treatment safety parameters were included.

Seven studies that met the inclusion criteria were identified:

<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>No. of patients</th>
<th>TXA dosing</th>
<th>Clinical outcome of interest</th>
<th>Primary efficacy outcome</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beauchene et al. [11]</td>
<td>Retrospective chart analysis</td>
<td>33</td>
<td>1–4 g IV or PO once</td>
<td>Efficacy, intubations, mortality, adverse effects</td>
<td>27 Patients had improvement TXA monotherapy</td>
<td>No adverse effects reported</td>
</tr>
<tr>
<td>Hasara et al. [12]</td>
<td>Retrospective cohort study</td>
<td>16</td>
<td>1 g IV once (one patient 100 mg IV once)</td>
<td>Intubation, mortality, adverse effects</td>
<td>14 Patients did not require intubation</td>
<td>No adverse effects reported</td>
</tr>
<tr>
<td>Martinez Manzano et al. [13]</td>
<td>Retrospective case series</td>
<td>11</td>
<td>1 g IV once</td>
<td>Length of stay, intubation, mortality, adverse effects</td>
<td>Mean length of stay, 1.2 day</td>
<td>No adverse effects reported</td>
</tr>
<tr>
<td>Du-Thanh et al. [14]</td>
<td>Retrospective study</td>
<td>35</td>
<td>1 g PO once, 3 g daily maintenance</td>
<td>Efficacy, adverse effects</td>
<td>23 Patients (out of 35) had decrease of duration and intensity of episode</td>
<td>1 Discontinued gastrointestinal intolerance</td>
</tr>
<tr>
<td>Wang et al. [15]</td>
<td>Case report</td>
<td>1</td>
<td>1 g IV once</td>
<td>Efficacy, adverse effects</td>
<td>Symptoms resolved</td>
<td>No adverse effects reported</td>
</tr>
<tr>
<td>Grewal et al. [16]</td>
<td>Case report</td>
<td>1</td>
<td>Not listed</td>
<td>Efficacy, adverse effects</td>
<td>Symptoms resolved</td>
<td>No adverse effects reported</td>
</tr>
<tr>
<td>Stoldt et al. [17]</td>
<td>Case report</td>
<td>1</td>
<td>1 g IV once</td>
<td>Efficacy, adverse effects</td>
<td>Symptoms resolved</td>
<td>No adverse effects reported</td>
</tr>
</tbody>
</table>

TXA, tranexamic acid; IV, intravenous; PO, per oral.
three were retrospective, one was a case series, and three were individual case reports. All studies commented on the general efficacy of TXA for bradykinin-mediated angioedema conditions and included information regarding intubation, mortality, and adverse effects.

The two largest retrospective studies [11,12] consisted of 33 and 16 patients, respectively. The primary outcomes were the time to the resolution of angioedema symptoms and the number of patients that required intubations. In the larger 33-patient retrospective cohort study [11], TXA was used as first-line therapy, with most patients (81.81%) showing significant improvement (regression of edema/dyspnea or other symptoms, not complete remission) with TXA treatment alone. Additional treatment with icatibant was required in 15.2% of patients and 3.0% needed C1 esterase inhibitor (C1-INH) concentrate after a partial resolution of symptoms with TXA monotherapy, suggesting some patients did not have an adequate resolution of symptoms. In addition, approximately 40% of patients reported improvement within 1 hour of TXA administration and there were no intubations, and no side effects or fatalities occurred. In the smaller 16-patient retrospective cohort study [12], 87.5% of the patients did not require intubations, with the other 12.5% receiving intubation before TXA administration. No patients reported worsening angioedema in this study, with 74% of patients experiencing partial resolution of symptoms following TXA infusion. The patients reported no adverse effects in this study as well.

A retrospective case series of 11 ACEI-IA patients treated with TXA [13] reported the median length of hospital stay was 1.2 days. Although this series reported two intubation cases, both patients were intubated before the administration of TXA. The mortality rate in this case series was 0%, with no reported adverse effects.

Another study [14] included 35 patients, of which 25 received TXA during an episode of bradykinin-related angioedema. TXA was well tolerated and led to at least a partial resolution of symptoms in 92% of patients, with 48% having complete resolution. Treatment failure and treatment discontinuation due to digestive intolerance occurred in two patients, respectively. Four patients were not treated with TXA due to thromboembolic contraindications. Although this study was not specific to ACEI-IA, a similar underlying mechanism in angioedema supports the pharmacological action of TXA in bradykinin-mediated angioedema [13].

In addition to the retrospective studies conducted, three additional case reports [15–17] have been published on TXA use in ACEI-IA. At least partial resolution of symptoms with no adverse effects, intubations, or mortality was reported. Additionally, two clinical studies [12,13] reported two cases, each requiring intubation due to ACEI-IA, but these patients were both intubated before TXA initiation.

**DISCUSSION**

The mechanism of action for TXA in the treatment of ACEI-IA is not well understood. However, blockage of plasmin activation by TXA contributes to its antifibrinolytic effect and is an important step in amplifying kallikrein (a precursor of bradykinin) activation. TXA prevents fibrin-induced inflammatory peptides and decreases the conversion of kininogen into bradykinin. C1 esterase activates plasma kallikrein and factor XIIa to allow downstream bradykinin development [8,18]. Further research is needed to clarify the exact mechanisms by which TXA exerts its therapeutic effects in this population.

There are currently no US Food and Drug Administration (FDA)-approved medications for treating ACEI-IA, and no current guideline recommendations are available for acute ACEI-IA treatment. Traditional treatment of ACEI-IA revolves around discontinuing the offending agent and providing symptom management. Agents that are traditionally used for “on demand” treatment of hereditary angioedema (HAE) include ecallantide, icatibant, plasma-derived nano-filtered C1-INH, and recombinant C1-INH with limited studies in the acute treatment of ACEI-IA. In line with the mechanism of ACEI-IA, ecallantide inhibits kallikrein, icatibant blocks bradykinin, and C1-INH inhibits the activity of C1 esterases [19–21].

Untreated angioedema can progress to a compromised airway and without acute management can lead to increased mortality [22,23]. Given the findings of recent retrospective cohort studies and case reports, TXA has shown clinical utility in an adequate resolution of symptoms and preventing angioedema progression to intubation. Our review suggests that most patients had partial or complete resolution of symptoms following TXA treatment, with few requiring intubation [11–17,24].

An additional clinical study evaluated TXA use as a maintenance treatment for nonhistaminergic angioedema in 37 patients, of which 18 were diagnosed with HAE and 19 were diagnosed with idiopathic angioedema [24]. These patients also did not respond to antihistaminic treatment (even at high doses) and complement treatment was not explored. Of the 19 patients, there were only three acute angioedema attacks in 6 months following TXA initiation, of which only one was severe. There were no cases of an increased number of attacks before TXA initiation.
There were six accounts of adverse effects, of which 66.66% were digestive adverse effects and 33.33% were dizziness [24]. Although these patients were not confirmed to have ACEI-IA, it suggests the potential of TXA for nonhistaminergic angioedema in confirmed cases of non-HAE. The higher prevalence of adverse effects can be attributed to routine prophylactic use; however, in the emergency setting for ACEI-IA, TXA is administered less frequently.

The dosage of intravenous TXA in studies varied from 500 mg to 4 g administered per event with most patients receiving 1 g intravenously [11–17,24]. This is similar to the typical prophylactic dose for HAE of 1 g twice daily in adults [25]. Additionally, TXA has a favorable safety profile, with many studies reporting no adverse effects after an acute infusion [12,14]. A pooled analysis of two randomized controlled trials over 947 cycles in 500 women for heavy menstrual bleeding found that subjects using oral TXA at 3,900 mg/day experienced at least one adverse reaction compared to placebo (208 of 232 [89.7%] vs. 139 of 122 [87.8%]) [26]. The most common adverse events include headache (50.4% vs. 46.8%), nasal and sinus symptoms (25.4% vs. 17.3%), and back pain (20.7% vs. 15.1%) [26]. While no thromboembolic events were reported in the articles evaluated, it is important to consider the benefit of avoiding intubation versus the potential risk of thrombotic events.

OTHER THERAPEUTIC AGENTS

Other currently used off-label treatment options for ACEI-IA include agents used commonly for hereditary angioedema, including icatibant, ecallantide, fresh frozen plasma infusions, and C1-INH. Icatibant, a competitive bradykinin B2 receptor antagonist, is FDA-approved for the treatment of acute attacks of HAE. However, studies of overall efficacy in its use in ACEI-IA are mixed [19,27]. A potential benefit of icatibant is that it does not require hepatic or renal impairment dose adjustment [28]. Thus, there is limited data supporting icatibant use in ACEI-IA. In addition, its relatively high cost and limited availability make it less appealing for emergency use [29].

Ecallantide is FDA-approved for HAE and has been used off-label for ACEI-IA with mixed efficacy data because there is no statistical difference against the placebo for improving discharge criteria [20,30]. Ecallantide is a parental recombinant protein inhibitor of kallikrein thought to decrease bradykinin production to resolve angioedema. Similar to icatibant, ecallantide has a relatively high cost and limited availability, bringing into question its clinical effectiveness in medical practice [31]. Some evidence suggests ecallantide has a higher rate of hypersensitive reactions that further complicate its use [20].

Fresh frozen plasma (FFP) infusions have been used for ACEI-IA and are effective because they contain kininase 2 and ACE to directly breakdown bradykinin. Case series have reported the successful use of FFP in resolving angioedema symptoms. FFP may be a favorable agent in emergency use given its availability and relatively low cost; however, the risks for FFP infusion, including transfusion-related acute lung injury, fluid overload, and allergic reactions, pose a potential safety concern [32]. Additionally, there are some reports of worsening angioedema following FFP infusion, presumably due to initial spikes of kallikrein substrates [20,33]. In addition, there is a lack of large randomized controlled clinical trials that evaluate FFP use in the acute setting of ACEI-IA.

Purified C1-INH (such as Berinert) inactivates plasma kallikrein and factor XIIa to prevent downstream bradykinin and has been used in HAE, with several case reports supporting its use in ACEI. C1-INHs have been shown to improve symptoms within 15 minutes of administration and up to 10.1 hours for complete resolution [8,21]. A case series reported that no patients receiving C1-INH required intubation, whereas five required intubation in the control group. Despite several successful case reports, no clinical trials are currently evaluating the use of C1-INH for ACEI-IA [33]. Its cost and lack of ready availability/access in the emergency department further limit its use.

CONCLUSION

Future randomized controlled trials of TXA use in ACEI-IA are needed to further support its efficacy and safety in this indication. There have been no direct comparator studies for ACEI-IA between different agents, and future studies will allow a better comparison of efficacy and adverse effects to optimize agent selection. Potential drawbacks to the use of TXA include the possibility of thrombotic events, adverse gastrointestinal effects, and a lack of large-scale studies that evaluate its use. ACEI-IA remains a key unmet medical need, accounting for approximately 30% to 40% of angioedema emergency department visits [1]. As the ACEI class of medications is ubiquitously used for hypertension, heart failure, diabetes, and kidney disease, patients should be advised on the signs and symptoms of angioedema. Additionally, the gaining popularity of combination medications, the “polypill”, may further increase total ACEI exposure. Prompt treatment of ACEI-IA is needed to prevent intubation and improve clinical outcomes.

In this literature review, we highlight the valuable role of TXA...
TXA for ACEI-induced angioedema

in reducing intubation rates and improving angioedema symptoms in ACEI-IA. Notably, there were no deaths reported, and four patients requiring intubation in the evaluated studies were all intubated before TXA administration. TXA use may be advantageous due to availability, lower cost, and low prevalence of adverse effects compared to other off-label medications currently used for ACEI-IA.

ARTICLE INFORMATION

Author contributions
Conceptualization: all authors; Investigation: GNP, TMT, AC; Resources: GNP, TMT; Supervision: BR, CM; Writing–original draft: GNP, TMT, AC; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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REFERENCES


A case report of point-of-care ultrasound directed thrombectomy: a reversible cause of cardiac arrest managed with extracorporeal membrane oxygenation cannulation

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Extracorporeal membrane oxygenation (ECMO) has been increasingly employed in the emergency department for patients with a potentially reversible cause of cardiac arrest. We present the case of a young female patient with an in-hospital cardiac arrest who was found to have severe right heart strain on point-of-care ultrasound (POCUS), suggesting a massive pulmonary embolism. Rapid bedside diagnosis using ultrasound expedited bedside cannulation and initiation of ECMO as a bridge to surgical thrombectomy, and ultimately the patient survived with full neurologic function. With its ready availability and increasing acceptance by consultants, POCUS should be incorporated into cardiac arrest algorithms as the standard of care to rule in thrombotic and obstructive causes of cardiac arrest.

Keywords: Thrombectomy; Heart arrest; Extracorporeal membrane oxygenation; Point-of-care ultrasound; Case reports

What is already known
Extracorporeal membrane oxygenation (ECMO) has been increasingly employed in the emergency department for patients with a potentially reversible cause of cardiac arrest, such as myocardial infarction and pulmonary embolism. If successful, ECMO cannulation allows time for diagnostic imaging and life-saving interventions such as cardiac catheterization or emergent thrombectomy.

What is new in the current study
With increased implementation of diagnostic bedside ultrasound by emergency physicians, consultants have begun to trust this modality of imaging and its bedside interpretation to direct care towards faster interventions for the patient.
INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) has been increasingly employed in the emergency department (ED) for patients with a potentially reversible cause of cardiac arrest, such as myocardial infarction and pulmonary embolism (PE). If successful, ECMO cannulation allows time for diagnostic imaging and life-saving interventions such as cardiac catheterization or emergent thrombectomy. Chen et al. [1] reported a 34.1% rate of survival to hospital discharge in patients who underwent in-hospital cardiac arrest (IHCA) and underwent extracorporeal cardiopulmonary resuscitation (ECPR) after 10 minutes of conventional cardiopulmonary resuscitation without return of spontaneous circulation (ROSC). The CHEER (Mechanical CPR, Hypothermia, ECMO and Early Reperfusion) trial by Stub et al. [2] showed a neurologic survival rate of 54% in 26 patients who were placed on ECMO during cardiac arrest. Additionally, the mean duration of cardiopulmonary resuscitation prior to initiation of ECMO is strongly correlated with survival. Table 1 [1–9] summarizes the survival to hospital discharge rates between ECMO and traditional CPR. One retrospective study of 133 ECMO patients found low flow time to be an independent predictor of mortality, with mean CPR duration of 49.6 ± 5.6 minutes for patients experiencing IHCA, compared to 72.2 ± 7.4 minutes for patients with out-of-hospital cardiac arrest [10].

Although not traditionally included in the Advanced Cardiac Life Support (ACLS) algorithms, point-of-care ultrasound (POCUS) has increasingly become the standard of care in the management of cardiac arrest. The challenge for emergency physicians in these cases is the rapid identification of an underlying cause, which can be difficult in patients with minimal history and hemodynamic instability which does not allow for cross-sectional imaging. With increased implementation of diagnostic bedside ultrasound by emergency physicians, consultants have begun to trust this modality of imaging and its bedside interpretation to direct care towards faster interventions for the patient. In this case, we demonstrate the important role POCUS played in identifying severe right ventricular dysfunction as a likely cause of the cardiac arrest and helped direct a decision for urgent ECMO cannulation in the ED.

CASE REPORT

The patient was a 39-year-old female with morbid obesity who presented to the ED via ambulance with nonspecific chest and abdominal pain. On initial evaluation, she was alert but with altered mentation and distress of unclear etiology. Her heart rate was 123 beats/min with a blood pressure of 123/52 mmHg. She had been placed by emergency medical services on 6 L/min of oxygen via nasal cannula with an oxygen saturation of 96%. After triage she was placed in a resuscitation room, where she was placed on cardiac monitoring and a peripheral intravenous line was established. An electrocardiogram performed at bedside was unremarkable aside from sinus tachycardia. However, at this time she was noted to be hypotensive, intravenous fluids were administered without significant improvement, and a norepinephrine infusion was initiated. Continued hypotension required escalating doses of vasopressor medications, ultimately requiring norepinephrine (30 μg/min), vasopressin (0.04 μg/min), and epinephrine (10 μg/min). A right internal jugular central line was placed. Point-of-care troponin was elevated at 0.209 ng/mL (upper limit of normal 0.04). Due to undifferentiated hypotension, a POCUS was performed which showed significant right ventricular dilation on the parasternal long axis (Fig. 1A) and septal flattening with “D” sign on parasternal short axis (Fig. 1B), concerning in this clinical picture for massive PE.

At this time, the PE response team was consulted, as well as the ECMO team given her worsening hypotension, severe right heart strain on ultrasound, and escalating vasopressor requirements. Shortly after ECMO team arrival, she experienced a cardiac arrest. During the 29-minute period of active CPR, she was given tissue plasminogen activator (tPA) 50 mg, and under ultrasound guidance, she was placed on femoral artery-femoral vein peripheral ECMO. She rapidly stabilized on ECMO and was taken for computed tomography pulmonary angiography, which revealed a near-occlusive saddle PE. The next day she was taken for thrombectomy with interventional radiology, which was not suc-

Table 1. Survival to hospital discharge rates of ECMO and traditional CPR

<table>
<thead>
<tr>
<th>Study</th>
<th>ECMO (%)</th>
<th>Traditional CPR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al. [1] (2008)</td>
<td>34.1</td>
<td>24.4</td>
</tr>
<tr>
<td>Shin et al. [4] (2013)</td>
<td>35.2</td>
<td>17.4</td>
</tr>
<tr>
<td>Stub et al. [2] (2015)</td>
<td>54.0</td>
<td>NR</td>
</tr>
<tr>
<td>Ouweneel et al. [5] (2016)</td>
<td>27.4</td>
<td>14.7</td>
</tr>
<tr>
<td>Dennis et al. [6] (2019)</td>
<td>44.0</td>
<td>NR</td>
</tr>
<tr>
<td>Yannopoulos et al. [7] (2020)</td>
<td>43.0</td>
<td>7.0</td>
</tr>
<tr>
<td>Rob et al. [8] (2022)</td>
<td>42.7+</td>
<td>1.2</td>
</tr>
<tr>
<td>Suveine et al. [9] (2023)</td>
<td>20.0</td>
<td>16.0</td>
</tr>
</tbody>
</table>

ECMO, extracorporeal membrane oxygenation; CPR, cardiopulmonary resuscitation; NR, not reported.

“A total of 23.9% in patients without prehospital return of spontaneous circulation treated with extracorporeal CPR and 61.5% in patients with prehospital return of spontaneous circulation. The mean of these two was reported here.
cessful due to the high burden of organized thrombus. This was followed by an open thrombectomy with cardiothoracic surgery, at which time a large thrombus was able to be removed from the pulmonary arteries (Fig. 2). She ultimately survived the procedure and during an extended hospital course she was able to be transitioned from ECMO to right ventricular assist device, and subsequently was decannulated and discharged to an acute rehabilitation unit with no neurological sequelae.

Ethics statement
Informed consent for publication of the research details and clinical images was obtained from the patient.

DISCUSSION

This case illustrates the importance of POCUS as a definitive diagnostic modality for emergent decision-making in the ED. In cases of critically ill patients who are not able to undergo cross-sectional imaging, POCUS may be the only means by which the decision is made to initiate life-saving measures such as ECMO or tPA in reversible causes of cardiac arrest. Making this diagnosis at bedside can bypass a time-consuming computed tomography scan and reduce rates of decompensation in the radiology department, while providing enough information to allow the ED physician to assemble a multidisciplinary team at the bedside.

The guidelines for management of PE from the American College of Emergency Physicians (ACEP) show that “the finding of right ventricular dysfunction on bedside echocardiography may be used as indirect evidence for presence of PE, although this technology or skill level is unavailable in most EDs” [11]. With the advent of emergency provider training in POCUS, ED providers can now easily screen for the presence of right heart strain at the bedside [12]. Both the 2020 American Heart Association (AHA) guidelines and the Korean CPR guidelines state that a physician experienced in ultrasound may use this as an adjunct as long as it does not interfere with standard CPR, with the caveat that the physician should use caution to avoid interruptions in compressions [13,14].

Several features may be identified on bedside echocardiograms to screen for patients at higher risk of mortality from PE. In this case, a parasternal short view revealed a grossly dilated right ventricle as well as interventricular flattening, also termed a “D” sign (Fig. 1B). In a retrospective analysis of 511 patients, Kurnicka et al. [15] found that all hemodynamically unstable patients with
PE had some degree of right ventricular dilation. Another important finding on bedside ultrasound is right heart thrombus. Both Torbicki et al. [16] and Rose et al. [17] evaluated the mortality and outcomes of patients found to have right heart thrombus on echo, finding a 21% mortality rate of those with a thrombus compared to 11% mortality of those without. Additionally, the mortality rate of those able to undergo thrombectomy with right heart thrombus compared to those who received thrombolytics alone decreased from 23.8% to 11.3%, with thrombolytics showing mortality benefit on multivariate analysis. These findings, in addition to McConnell’s sign and reduced tricuspid annular plane systolic excursion can provide evidence of right heart strain to ED physicians and consultants to allow for faster recognition of massive PE and improve mortality rates. These sonographic findings of right heart strain are summarized in Fig. 3.

Currently, POCUS is not included in the traditional AHA guidelines for ACLS algorithm. International PE management guidelines do recommend use of ultrasound in hemodynamically unstable patients with suspected PE [18]. With its ready availability and increasing acceptance by consultants, bedside cardiac echocardiography should be incorporated in cardiac arrest algorithms in order to fully evaluate the patient for thrombotic or obstructive causes of cardiac arrest, including massive PE and pericardial effusion. If these are identified quickly, there is demonstrated benefit in initiating ECMO in the ED.

ECMO has been demonstrated to be successful in select patients who experience cardiopulmonary arrest secondary to massive PE as a bridge to definitive intervention [19]. Chen et al. [3] performed an observational study and propensity analysis comparing survival rates in patients with IHCA, finding a survival rate of 23.7% in those receiving ECPR compared to 10.7% of those receiving traditional CPR. This may reflect some selection bias as those chosen for ECPR are typically younger with potentially reversible causes of cardiac arrest [20]. Another meta-analysis showed a 13% absolute risk difference in survival to hospital discharge, favoring ECPR [4]. In nine selected studies involving both IHCA and out-of-hospital cardiac arrest (OHCA), initiation of ECMO demonstrates almost double the survival rate compared to conventional CPR (Table 1) [1–9].

A series of recent studies have investigated the use of ECMO in the ED with diverse results. The ARREST (Advanced Reperfusion Strategies for Refractory Cardiac Arrest) trial enrolled 30 patients with OHCA and refractory ventricular fibrillation. They found that 1 of 15 patients (7%) in the ACLS-only group survived to hospital discharge compared to 6 of 14 (43%) in the ECMO-facilitated resuscitation group. The trial was terminated early due to the sig-

<table>
<thead>
<tr>
<th>POCUS finding</th>
<th>Description</th>
<th>Image</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right ventricular dilation</td>
<td>Enlargement of the right ventricle due to increased right ventricular pressure</td>
<td><img src="image1.png" alt="Image" /></td>
</tr>
<tr>
<td>&quot;D&quot; sign</td>
<td>Flattening of the interventricular septum</td>
<td><img src="image2.png" alt="Image" /></td>
</tr>
<tr>
<td>Tricuspid annular plane systolic excursion</td>
<td>Decreased excursion of the tricuspid annular plane during systole (defined as &lt;16 mm), indicating right ventricular akinesia</td>
<td><img src="image3.png" alt="Image" /></td>
</tr>
<tr>
<td>Right heart thrombus</td>
<td>Thrombus extending from pulmonary vasculature into the right heart</td>
<td><img src="image4.png" alt="Image" /></td>
</tr>
</tbody>
</table>

Fig. 3. Point-of-care ultrasound (POCUS) findings of right heart strain.
significant superiority in the ECMO group [7]. A larger trial, the Prague OHCA trial, found a 180-day survival rate of 1.2% in patients without prehospital ROSC treated with conventional ACLS and 23.9% in patients without prehospital ROSC treated with ECPR, concluding a benefit to those with OHCA without prehospital ROSC [8]. Most recently, Suverein et al. [9] performed a trial of patients with OHCA, finding that 14 of 70 patients (20%) in the ECPR group survived with favorable neurologic outcome, versus 10 of 62 in the conventional CPR group, finding no statistical difference in neurologic outcome.

Although ED ECMO is still under ongoing clinical investigation, there is literature to support the benefit of ED ECMO in select patients. In these cases, every effort must be made to identify the cause of the cardiac arrest and in suitable candidates, rapid placement on ECMO is advisable. The ability to perform POCUS to identify these causes efficiently can add an important role in the decision-making and survival of these patients.

ARTICLE INFORMATION

Author contributions
Conceptualization; AP, MH; Formal analysis; all authors; Project administration; AP, MH; Writing—original draft: all authors; Writing—review & editing: all authors. All authors read and approved the final manuscript.

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Data availability
Data sharing is not applicable as no new data were created or analyzed in this study.

REFERENCES


CONCEPT AND DEFINITION OF THE METAVERSE

A "metaverse" is a virtual world or universe that is fully immersive, interactive, and persistent, where users can create their own digital avatars, interact with each other, and participate in various activities and experiences. It is often described as a fully realized version of the internet, where the virtual world is seamlessly integrated with the physical world and allows users to transcend the limitations of space and time. In a metaverse, users can create, own, and trade digital assets, such as virtual real estate, virtual currency, and other virtual objects [1]. They can also participate in social interactions, such as attending virtual events, playing games, and collaborating on projects [2].

Such concepts have been popularized by science fiction [3], such as Neal Stephenson’s Snow Crash, which depicts a virtual reality universe called the "Metaverse," and Ernest Cline’s Ready Player One, which is set in a dystopian future where people spend most of their time in a virtual world called the "OASIS." While the idea of the metaverse is young, several companies and developers are actively working on creating metaverse platforms, incorporating technologies such as virtual reality, augmented reality, and blockchain. They believe that the metaverse has the potential to transform the way people interact with each other and the world around them, and may become a significant part of our daily lives in the future.

A MIRROR WORLD METAVERSE HOSPITAL FOR ENHANCING ACCESS TO HEALTHCARE SERVICES

Our goal in this project was to establish a hospital in the metaverse by creating a virtual, digital twin of a real hospital. To do so, there are several considerations. First, it is imperative that communication takes place not only using avatars or characters, but also through the incorporation of video conference capabilities to enable seamless, face-to-face interactions. Secondly, due to the nature of hospital processes, it should be possible to hold conferences, virtual meetings, seminars, and other similar events to facilitate communication among participants. Lastly, it is
crucial to ensure that many stakeholders, including patients, medical staff, and visitors, can participate in the metaverse space at the same time.

Conventionally, metaverses are categorized into four distinct types: lifelogging, augmented reality, virtual reality, and mirror world (Fig. 1) [4–6]. Two additional ways to analyze the metaverse consider external dimensions and intimate dimensions. The external dimension covers activities that happen in the surrounding world, whereas the intimate dimension relates to personal and subjective experiences.

Overall, each metaverse platform has its own unique functions and features, but they all aim to provide users with immersive and interactive virtual experiences.

The metaverse hospital described in this study was specifically designed to be easily accessible to all users and utilizes a mirror world design to resemble the real-life Chosun University Hospital (CUH; Gwangju, Korea). To create a medical metaverse hospital with high patient accessibility, it was necessary to identify a platform that could create a customized virtual space within a metaverse that allowed face-to-face communication between doctors and patients. ZEP (ZEP Co Ltd; https://zep.us/) is a metaverse platform that accommodates up to 50,000 simultaneous participants, emphasizes two-dimensional pixel art, and creates domains for each page, facilitating the construction and operation of metaverse spaces. The platform enables easy communication through video, audio, and text messages and one-click access to metaverse spaces on a web browser. As a web-based platform, ZEP is convenient to use on personal computers, and in-app functions can be easily coded based on JavaScript. Our goal was to improve connections between users and the hospital using the metaverse, creating an improved intimate dimension.

**PURPOSE OF METAVERSE HOSPITAL**

As part of the fourth industrial revolution [7], the development of technologies such as artificial intelligence, big data, information communication technology (ICT), and the explosive development of the Internet led to active exchanges across borders and rapid

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**Fig. 1.** The four types of metaverse. 3D, three-dimensional. Based on Smart et al. [4], Milgram et al. [6], and Chengoden et al. [6].
globalization of the service industry. The medical service industry is also rapidly changing with the acceleration of globalization. Korea has exhibited the best performance for most medical indicators (avoidable mortality, treatable mortality, infant mortality, life expectancy, and preventable mortality) among Organization for Economic Cooperation and Development (OECD) countries [8]. Due to the excellent medical standards and services in Korea, the number of "medical tourists" traveling to the country is increasing rapidly. In addition, increasing numbers of foreign medical staff are visiting Korea for medical training. However, as the COVID-19 pandemic encouraged social distancing, the medical service industry has been characterized by a growing number of telemedicine companies worldwide.

As the demand and necessity for non-face-to-face medical services increased, new medical services incorporating information technology (IT) were required. Therefore, CUH established a metaverse platform to provide medical services via IT and promote medical tourism. First, it provides useful and enjoyable content to attract more users. Second, it improves human-computer interactions through an intuitive user experience and design interface. Third, it increases efficient provision of medical services such as a virtual map, transportation reservations, and real-time communications with hospital staff members. Finally, the platform promotes medical education users, who may include patients, students, doctors, nurses, or medical staff from abroad. Creating the CUH Metaverse took over 1 year, and a team of more than 10 people were involved in its development.

**UTILIZATION OF DIGITAL TWIN AT CUH**

**Simulation of traveling to Gwangju to give favorable impression to CUH medical tourism**

Metaverse content that simulates traveling from abroad to Incheon International Airport (Incheon, Korea), then to Gwangju Korea Train Express (KTX) station, and finally to CUH was established to bridge the psychological distance between patients and the hospital (Fig. 2). The airport’s and KTX station’s metaverse pages provide a ticket reservation function and a clear guide for traveling to CUH. The objective of the tour guide simulation is to provide favorable impressions of CUH to patients by closely resembling the real world and creating a sense of familiarity. Foreign patients or doctors can access the metaverse at any time before, during, and after their hospital visit. Upon accessing the metaverse after arriving at Incheon International Airport, they will be greeted by avatars that provide welcoming messages and information about the hospital and transportation in real time.

This feature allows users to quickly address any difficulties or questions they may encounter during the transportation process. Additionally, virtual galleries, history halls, and gaming activities are provided in the metaverse to alleviate potential boredom during the journey. Information about diseases, medical procedures, medication, and other services offered by the hospital may also be found in the metaverse.

**Building a global network of metaverse hospitals**

CUH has recently launched an international medical training initiative for doctors from many nations, including Mongolia, Russia, and Saudi Arabia. The initiative, established under the supervision of the Korean Ministry of Health and Welfare, aims to provide participants with invaluable learning experiences at CUH medical training programs. Implementation of metaverse digital twins for participating hospitals has made it easy to encourage global collaborations. The establishment of an international healthcare center in the metaverse revolutionizes the concept of patient care. The internal space of the virtual center is meticulously designed to replicate the physical environment of a hospital, complete with lifelike structures, furniture, and spaces (Fig. 3). This virtual space creates a sense of realism and enables patients to engage in direct communication with the center’s staff from anywhere at any time. Through this innovative approach, CUH strives to bridge geographical barriers, making healthcare accessible and convenient for patients around the globe. The Middle East Clinic, an integral part of the hospital’s global system, addresses the specific needs of Middle Eastern patients. Recognizing the importance of private and confidential communication, the clinic offers separate spaces in each department for one-on-one interactions. This design fosters a comfortable environment that respects cultural norms and ensures patients feel at ease while discussing their health concerns. Moreover, understanding the value of collaboration and knowledge sharing among clinicians, a dedicated space for holding meetings and seminars has been created within the metaverse. Demonstrating its commitment to religious inclusivity, the Middle East Clinic also has a virtual prayer room that recognizes and respects Islamic religious practices, which entail five daily prayers. By providing this designated space, CUH showcases its understanding and appreciation for diverse faiths, further enhancing patient comfort and satisfaction.

By developing a metaverse global hospital network and collaboration, CUH aims to enhance the knowledge of healthcare professionals, improve the hospital’s reputation, and further expand its global network. Ultimately, CUH expects to overcome its geographical limitations and be in the center of the largest virtual
Fig. 2. Virtual space experience service system for strengthening psychological accessibility in the Chosun University Hospital (Gwangju, Korea) Metaverse. (A) Airport entrance. (B) User guide. (C) Bus reservation link. (D) Train ticket reservation link. (E) Guide to using the keyboard. (F) Quiz game. (G) Gwangmyeong station. (H) Gwangju Songjeong station.
Introduction and application of a ZEP-based metaverse hospital

Fig. 3. Network expansion through global system diversification in the Chosun University Hospital (Gwangju, Korea) Metaverse. (A) International Healthcare Center. (B) Middle East Clinic. (C) Meeting room. (D) Seminar room. (E) Lecture room. (F) Prayer room.

medical complex in the world, which includes hospitals from Mongolia, Russia, Saudi Arabia, Thailand, the United Kingdom, and the United States.

Overcoming physical constraints of the real world through implementation of imaginary space within a digital twin Hospitals have long recognized the significance of cultural spaces in improving the overall well-being of patients and their families, offering a respite from anxiety and stress. However, the constraints of physical space often hinder the creation of diverse cultural environments within healthcare facilities. CUH found an innovative solution in the form of the metaverse. By leveraging this immersive virtual platform, CUH has reimagined the concept of hospital space, offering a range of culturally enriching experienc-
es to enhance hospital visits for patients and visitors alike (Fig. 4).

One of the key initiatives undertaken by CUH is the establishment of a virtual gallery within the metaverse, enabling the public to indulge in art and creativity by providing a platform for local artists to showcase their works, fostering a vibrant cultural atmosphere and stimulating positive emotions. By transcending physical limitations, the hospital extends the reach of artistic expression and contributes to the well-being of patients and their families. In addition to the gallery, the hospital created a history hall within the metaverse, inviting visitors to delve into the rich past of the institution. This virtual space serves as a repository of the hospital’s heritage, showcasing its milestones and achievements. Patients and their families can explore the hospital’s journey, gaining a deeper understanding of its commitment to excellence and a sense of pride in being a part of its legacy. Recognizing the importance of local tourism and community engagement, CUH has also established a content hall within the Metaverse, offering valuable information about the surrounding area. This digital space serves as a hub for sharing tourist attractions, local culture, and events, enabling patients and visitors to immerse themselves in the local community within the hospital environment.

Fig. 4. Overcoming physical environmental constraints by implementing space beyond reality in the Chosun University Hospital (Gwangju, Korea) Metaverse. (A) The Snail Gallery. (B–D) Content Hall. (B) Tourist Hall. (C) History Hall. (D) Introduction of medical staff. (E) Martin Luter King Hall. (F) Lobby.
CUH is taking patient empowerment to the next level with the introduction of a dedicated specialist hall, aimed at allowing patients to choose their caregivers from among the hospital’s renowned medical staff. By showcasing detailed profiles and accomplishments of these professionals, the specialist hall provides patients with the information they need to make informed decisions about their healthcare providers. This transparent approach gives patients greater control over their medical journey and fosters stronger patient-caregiver relationships based on trust. Through the specialist hall, patients can explore the diverse range of medical disciplines offered by the hospital and select caregivers who best align with their specific needs and preferences.

Through these innovative uses of the metaverse, CUH has revolutionized the hospital experience, transcending physical limitations and providing culturally diverse spaces that promote well-being and engagement. By embracing virtual technology, the hospital has overcome the constraints of physical space and created a platform for artistic expression, historical exploration, community connection, and professional growth.

**Improving service satisfaction by providing location information services**

CUH has undertaken an innovative approach to address the challenges of navigating a complex healthcare facility. As hospitals grow in size and complexity, finding specific hospital locations can be a daunting task, leading to increased patient stress, prolonged hospital stays, and reduced service satisfaction. Traditionally, hospitals have employed solutions such as location notices, assistants, signs, and maps to aid patients in navigating their premises. However, these methods often fall short, leaving many individuals still struggling to find their way, especially during their initial visits.

To address this issue, CUH has embraced an advanced solution by implementing a real-life space within the metaverse, focusing on outpatient departments and examination rooms that witness significant movement (Fig. 5). By accessing the CUH Metaverse, patients can now virtually explore the outpatient departments and examination rooms situated on the first and second floors of the hospital. Crucially, comprehensive location information is readily available at all stages: before, during, and after the hospital visit. This integration of actual structure and location within the metaverse aims to enhance service satisfaction by minimizing the time spent wandering and reducing hospital stay durations. This technological approach not only streamlines the patient navigation process but also contributes to an overall improvement in the hospital experience. Patients can familiarize themselves with the hospital layout and confidently navigate to their desired destinations, eliminating stress and uncertainty associated with finding specific medical departments. Through the utilization of the metaverse and the provision of accurate location information, CUH aims to significantly enhance patient satisfaction, reduce hospital stays, and optimize resource utilization.

**DISCUSSION**

The CUH Metaverse was designed to promote medical tourism. First, it provides useful and enjoyable content to attract more users. Second, it improves human-computer interactions through a more intuitive user experience and design interface. Third, it increases efficiency in medical services by providing a virtual map, transportation reservation, and real-time communication with hospital staff members. Finally, the platform promotes medical education to users, who could be patients, students, doctors, nurses, or medical staff from abroad. However, several challenges...
remain to be overcome. Further research is imperative, encompassing the measurement of patient satisfaction, user experience (UX) and user interface (UI) usability tests, privacy issues in video recordings, and other legal issues associated with telemedicine. In the end, establishing a global standard for constructing metaverse hospitals would be necessary to build a more convenient and integrated platform.

The metaverse brings with it the promise of revolutionizing the practice of medicine, ushering in a new era of accessible, efficient, and effective healthcare for both patients and medical professionals. CUH’s digital metaverse twin on ZEP is at the forefront of this transformation, facilitating seamless interactions among doctors, enabling international collaborations, and providing video consultations for medical tourists. CUH is breaking down geographical barriers and bridging healthcare disparities around the world. Doctors can collaborate effortlessly, exchanging knowledge and expertise, ultimately leading to improved patient care and outcomes. Additionally, the metaverse enables video consultations, allowing medical tourists to receive healthcare services without the need for physical travel.

The convergence of emergency medicine and the metaverse holds immense implications for the healthcare industry. Utilizing metaverse simulations in emergency medicine training presents a controlled and secure environment for medical professionals to refine skills, potentially minimizing errors in emergency care and enhancing patient outcomes. Moreover, the metaverse improves access to emergency medical services in remote or underserved areas, leading to more efficient emergency response protocols. Finally, the metaverse provides a dashboard of empty beds among emergency rooms in participating hospitals, enabling patients and rescuers to easily locate available spaces during emergencies.

Just as the internet surpassed its initial purpose of static websites and became a foundation for various industries, the concept of the metaverse encompasses more than just a singular technology or digital space. The evolution of technologies like extended reality, blockchain, digital twins, and edge computing is giving rise to metaverse platforms such as Gather (Gather Presence Inc), Meta Horizon Worlds (Meta), Roblox (Roblox Corp), The Sandbox (Pixowl), Second Life (Linden Lab), and ZEP. A metaverse hospital that can be utilized across various platforms is desirable, rather than developing a metaverse digital twin hospital limited to a single platform, as metaverse platforms will continue to evolve. Ultimately, regardless of the platform used, the establishment of a healthcare metaverse requires a deep understanding of healthcare systems, robust data security measures, and strong networks with healthcare institutions. Therefore, it is anticipated that healthcare metaverse expertise will gradually increase.

CONCLUSION

The potential of the metaverse in healthcare extends far beyond CUH’s pioneering efforts. From virtual reality simulations for medical training to remote patient monitoring and telemedicine, the metaverse has the power to reshape the entire healthcare landscape. By harnessing the capabilities of this immersive digital realm, the future holds the promise of enhanced accessibility, personalized care, and optimized healthcare delivery. However, as with any transformative technology, challenges and considerations lie ahead. Security, privacy, and standardization are crucial factors that must be addressed to ensure the safe and ethical implementation of the metaverse in healthcare. Ongoing research, collaborations, and regulation will be necessary to unlock the full potential of this paradigm-shifting technology.

In conclusion, the metaverse hospital exemplifies the transformative potential of merging technology and healthcare. CUH’s metaverse digital twin serves as a testament to the possibilities of improved collaboration, global connectivity, and enhanced patient care. In the near future, CUH will announce the world’s first fully functioning hospital in virtual reality. As the metaverse continues to evolve, the future of medicine promises a healthcare landscape that is more interconnected, accessible, and patient-centric than ever before.

ARTICLE INFORMATION

Author contributions
Conceptualization: MRK, YK; Data curation: KJK; Formal analysis: JYC; Investigation: MRK, YK; Methodology: MRK, HJN; Project administration: YK; Supervision: YK; Visualization: MRK, HJN; Writing--original draft: MRK; Writing--review & editing: JYC, HJN, KJK, YK. All authors read and approved the final manuscript.

Conflicts of interest
The authors have no conflicts of interest to declare.

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Data availability
Data analyzed in this study are available from the corresponding author upon reasonable request.
REFERENCES


An otherwise healthy woman in her 50s presented to the emergency department with a 7-day history of odynophagia and posterior neck pain, radiating to the occipital region and worsening with movement. No fever or cervical stiffness was noted. Her C-reactive protein level was high (112 mg/L), and her white blood count was 12,800/µL.

At first, a carotid or vertebral artery dissection was considered as the probable diagnosis, but it was excluded by computed tomography (CT) angiography. Neck CT and magnetic resonance imaging (MRI) exams were performed later (Figs. 1, 2) and confirmed the diagnosis of acute calcific tendinitis of the longus colli muscle (ACTLCM). In retrospect, the imaging findings revealed that the characteristic features of ACTLCM had been overlooked on the initial CT angiography exam.

ACTLCM is a rare, self-limited condition characterized by calcium deposition in the superior oblique tendon fibers of the longus colli muscle and a secondary inflammatory reaction. Typical symptoms are acute-onset odynophagia, neck pain, and stiffness; other symptoms include limited cervical range of motion, occipital headache, trismus, and low-grade fever. These symptoms can be misdiagnosed as meningitis or another life-threatening condition such as retropharyngeal abscess or infectious spondylitis. Dysphagia, odynophagia, and the absence of photophobia are clinical aspects more often associated with retropharyngeal processes, and they can help differentiate ACTLCM from meningitis [1]. Specific imaging findings include amorphous calcifications anterior to the C1–C2 vertebrae with adjacent soft-tissue edema and fluid collection in retropharyngeal space, and they can help to exclude spondylitis and retropharyngeal abscess. CT and MRI are preferable to radiographs. Treatment includes immobilization, analgesics, and non-steroidal anti-inflammatory drugs, as well as corticosteroids in severe cases. Symptoms usually resolve within 2 weeks. This patient received analgesics, corticosteroids, and a cervical collar, and the symptoms resolved in 5 days. Early and accurate diagnosis is the key to proper patient management [2–4].

What is already known
Acute calcific tendinitis of the longus colli muscle is a rare, benign, and self-limited condition characterized by acute-onset neck pain, neck stiffness, and odynophagia.

What is new in the current study
This case highlights how acute calcific tendinitis of the longus colli muscle can mimic the clinical presentation of neck arterial dissection, potentially resulting in a failure to recognize acute calcific tendinitis in initial cross-sectional imaging examinations focused on blood vessels.
Ethics statement
All personal data were removed, and images were entirely anonymized.

ARTICLE INFORMATION

Author contributions
Conceptualization: RML; Investigation: all authors; Project administration: DVS; Supervision: DVS; Visualization: DVS; Writing-original draft: all authors; Writing-review & editing: all authors.
All authors read and approved the final manuscript.

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Data sharing is not applicable as no new data were created or analyzed in this study.

REFERENCES

Unraveling the link between severe bradycardia and paraquat poisoning

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Dear Editor,

Poisoning with paraquat, a highly lethal herbicide, is often encountered in developing countries [1]. Human intoxication by paraquat typically occurs due to ingestion either accidentally or with suicidal intent and rarely following dermal exposure [2]. The high case fatality rate is due to lack of an effective antidote and the inherent cellular toxicity of paraquat, which is secondary to oxidative stress [3,4]. The typical clinical presentation includes multiorgan failure involving the gastrointestinal, hepatorenal, and respiratory systems [5]. Paraquat-induced pulmonary fibrosis has been abundantly reported in the literature, with evidence of its mechanism, clinical manifestation, and treatment strategies [6]. However, little to no evidence exists on the hemodynamic and cardiac electromechanical effects of acute paraquat poisoning [7]. Cases of extreme bradycardia following paraquat poisoning are particularly rare [8]. We report a case of bradycardia that was refractory to anticholinergics, which is an unusual clinical manifestation of acute paraquat poisoning.

A 32-year-old man with no known comorbidities had previously presented with an alleged history of approximately 30 mL of 20% paraquat consumption with an intent to commit suicide. The patient was treated elsewhere primarily with gastric lavage and arrived at GSL Medical College and Hospital (Rajamahendravaram, India) 14 hours postconsumption. On arrival, the patient had typical mucosal involvement and was febrile with a temperature of 38.3 °C. His heart rate was 110 beats/min, his respiratory rate was 28 breaths/min, and his oxygen saturation was 90% on ambient room air. Systemic examination findings were unremarkable, except for bibasal crepitations over both lung fields. Investigations revealed deranged kidney function tests suggestive of acute kidney injury and elevated transaminases. The patient was administered antioxidant therapy (N-acetylcysteine, vitamin C, vitamin E), immunosuppressants (parenteral steroids, 8 mg dexamethasone intravenously every 8 hours for the first 72 hours), antacids, and a topical local anesthetic for mucosal erosions, along with other supportive therapy. Renal replacement therapy was initiated on day 2 of hospitalization because of declining renal function (metabolic acidosis, 7.24 pH; oliguria, urine output of 600 mL/24 hr; incremental trend in urea and creatinine levels, 96 and 4.8 mg/dL, respectively). In addition, his oral mucosal lesions worsened, and he developed dysphagia within 48 hours of hospitalization. Enteral feeding through a nasogastric tube was established, and other supportive measures were continued. Serial evaluations of hepatorenal function with hematological testing and close monitoring of clinical conditions
were carried out in the intensive care unit. On day 3 of hospitalization, the patient developed severe bradycardia, with his heart rate dropping to 35 beats/min. The chronotropic agents glycopyrrolate and atropine were administered parenterally. Although we noted a transient improvement in heart rate following the administration of these agents, the increase was not sustained. A 12-lead electrocardiogram suggested sinus bradycardia, and the echocardiogram was normal. Serum electrolytes were within normal limits. A thyroid profile was carried out and revealed T3 of 0.77 nmol/L, T4 of 102 nmol/L, and thyroid stimulating hormone (TSH) of 0.60 IU/mL.

Low-dose thyroxine therapy was initiated at a dose of 50 μg/day, and a sustained increase in heart rate was noted. The patient was subjected to three sessions of hemodialysis during hospitalization. The patient’s hypoxemia worsened by day 5 of hospitalization, with an ambient air saturation nadir of 88%, which improved on subsequent days without oxygen therapy. A chest roentgenogram revealed early lung fibrosis, although the serial evaluation did not show further clinical and radiological worsening. The patient’s heart rate normalized, oxygenation improved, and acute kidney injury resolved by day 7 of hospitalization. The patient was observed in a step-down unit for 1 week and then discharged home following an uneventful observation period after normalization of his hepatorenal functions. He was discharged normoxemic in an ambulant, cheerful condition following psychiatric counseling. Thyroxine supplementation was stopped after 1 week. The patient was reviewed 1 week later and was asymptomatic, with normal vitals and an unremarkable systemic examination.

Paraquat is a quaternary nitrogen herbicide that triggers oxidative stress, mitochondrial damage, and multiorgan injuries, including the heart. Cardiotoxicity has been investigated in several experimental studies following paraquat exposure in rodents [7,9,10]. Acute paraquat poisoning has adverse hemodynamic and electromechanical effects on rat hearts. Decreases in heart rate, blood pressure, and cardiac contractility have been noted in a dose-dependent manner in anesthetized rodents [7].

Paraquat toxicity has both direct and indirect effects on the cardiovascular system. Significant contractile dysfunction has been observed following direct cardiac injury, as shown by reduced fractional shortening and myocardial remodeling. Reactive oxygen species exert indirect effects by causing ischemic alterations in the heart. Ventricular myocyte models in rodents have shown that altered calcium transport systems may be responsible for the cardiac dysfunction caused by paraquat. [10]. Paraquat poisoning can lead to toxic myocarditis and sinus node dysfunction [11]. All these effects could have contributed to our patient’s bradycardia following paraquat poisoning. Another possible explanation is that immunosuppression with large doses of glucocorticoids may reduce basal TSH level, resulting in low thyroid hormone levels that may produce bradycardia [8]. Low thyroxine may impair ventricular function and the neuroendocrine profile in people with preexisting heart conditions [12]. Our patient developed extreme bradycardia on day 3 of hospitalization, which could be attributed to paraquat cardiotoxicity, to the glucocorticoid effects used in therapy, or to both. Failure to respond to the parasympatholytic drug atropine prompted us to initiate thyroxine therapy after evaluating the patient’s thyroid profile. The patient made a remarkable clinical recovery following thyroxine therapy and was discharged home.

No antidote is available for paraquat poisoning, so clinicians often resort to antioxidants and immunosuppressive agents. Adverse effects of acute large doses of immunosuppressive therapy, such as infection or hyperglycemia, can occur when treating a case of acute paraquat toxicity. Physicians should have high suspicion of possible cardiotoxicity when treating such a case. They should manage these patients swiftly with symptomatic and supportive therapy, as mortality in this subset is extremely high.

Ethics statement
The patient provided written informed consent for publication of the research details.

ARTICLE INFORMATION

Author contributions
Conceptualization: AR, TM, RE; Investigation: RE, YVC, KH, SM, GR; Methodology: AR, RE, YVC, KH, SM, GR; Validation: TM; Visualization: TM; Writing–original draft: AR, RE; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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REFERENCES