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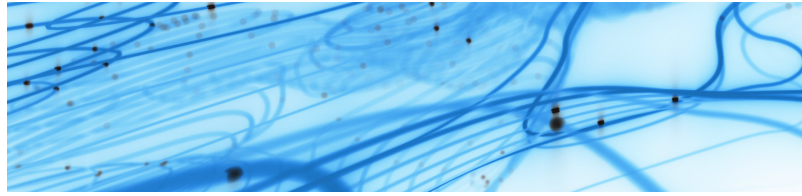
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**Editorials**

- 125** **Simulation: past, present, and future**  
Benjamin Worth Berg
- 129** **Data integration using information and communication technology for emergency medical services and systems**  
Ji Hoon Kim

**Review Articles**

- 132** **Current challenges in adopting machine learning to critical care and emergency medicine**  
Cyra-Yoonsun Kang, Joo Heung Yoon
- 138** **To resuscitate or not to resuscitate? The crossroads of ethical decision-making in resuscitation in the emergency department**  
Nirdosh Kumar, Meraj Fatima, Sara Ghaffar, Faysal Subhani, Shahan Waheed
- 147** **A clinical approach to an unidentified aerosolized bioterrorism agent: a narrative review for emergency providers**  
Rashed Alremeithi, Natalie Sullivan, Hannah Checkeye, Maryann Mazer-Amirshahi, Ali Pourmand

**Systematic Review**

- 157** **Mortality among adult patients with sepsis and septic shock in Korea: a systematic review and meta-analysis**  
Myeong Namgung, Chiwon Ahn, Yeonkyung Park, Il-Youp Kwak, Jungguk Lee, Moonho Won

**Original Articles**

- 172** **Hyponatremia and hypernatremia in the emergency department: severity and outcomes**  
Karalynn Otterness, Adam J. Singer, Henry C. Thode Jr, W. Frank Peacock
- 181** **Usability testing of a blind intubation device for intubation novices: a randomized crossover simulation study**  
Dae Kon Kim, Yu Jin Kim, Joo Jeong, Yoon Ha Joo, You Hwan Jo, Seung Min Park
- 191** **The effect of regional distribution of isolation rooms in emergency departments on ambulance travel time during the COVID-19 pandemic**  
Soo In Lee, Sae Byel Kang, Sun Young Lee, Dong Sun Choi

- 200** **Chronic juvenile stress exacerbates neurobehavioral dysfunction and neuroinflammation following traumatic brain injury in adult mice**  
Sung-Jin Park, Hyun-Jeong Park, Backyoun Kim, Young-Min Kim, Suk-Woo Lee, Hoon Kim
- 213** **Uncooperative patients suspected of acute stroke ineligible for prehospital stroke screening test by emergency medical service providers: final hospital diagnoses and characteristics**  
Sol Han, Sung Wook Song, Hansol Hong, Woo Jeong Kim, Young Joon Kang, Chang Bae Park, Jeong Ho Kang, Ji Hwan Bu, Sung Kgun Lee, Seo Young Ko, Soo Hoon Lee, Chul-Hoo Kang
- Brief Research Report** **224** **Utilization of point-of-care ultrasound among graduates of a 4-year longitudinal medical school ultrasound curriculum**  
Andy Phan Nguyen, Soheil Saadat, Michelle Thao Nguyen, Monica Devang Desai, Jonathan Wesley Rowland, John Christian Fox
- Case Report** **230** **The usual sedative dose in very elderly patients with a good neurological outcome after cardiac arrest can cause a suppressed background and burst suppression: two case reports**  
Jae Hoon Lee
- Commentary** **235** **Digital healthcare: the new frontier of holistic and efficient care**  
Dongchul Cha
- Image** **238** **Hyperacute presentation of fat embolism syndrome after multiple long bone fractures**  
Yong Nam In, Se Kwang Oh, Jin Hong Min
- Correspondence** **241** **Treatment with Vitis vinifera extract for controlling ascites and local swelling in snakebites**  
Yong Nam In, Se Kwang Oh, Jin Hong Min, Jung Soo Park, Yeon Ho You, Insool Yoo, Seung Whan Kim, Jinwoong Lee, Seung Ryu, Won Joon Jeong, Yong Chul Cho, Hong Joon Ahn, Chang Shin Kang

**246 Eosinophilic granulomatosis with polyangiitis presenting as recurrent myocardial infarction**

Giulia Vinco, Marco Aroldi, Michele Romano, Marilena Frigato, Alfredo Fede, Cristian Fava,  
Maria Teresa Costantino, Corrado Lettieri

**249 Optic nerve sheath diameter measurement by ultrasound after moderate traumatic brain injury**

Mario Graziano, Danilo Biondino, Isabella Fioretto, Andrea Valerio Marino



# Simulation: past, present, and future

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## THE PAST: WHAT WE HAVE LEARNED ABOUT SBHE

Simulation-based healthcare education (SBHE) is a widely used method for teaching and assessing novice to advanced learners' clinical skills, teamworking, interprofessional healthcare skills, and more, in many disciplines [1-3]. Experience, knowledge, and empirical research have incrementally guided growth of effective methods and techniques. As an example of iterative progress, early simulation-based education in anesthesia sought to present learners with realistic real-time representations of intraoperative care [4]. Experience with this approach revealed that real-time representation of entire surgical cases was impractical and unnecessary to reach teaching and learning objectives. Time-compression became a standard approach in the design of many simulation scenarios.

In emergency medicine SBHE was first focused on resuscitation and has expanded to include evidence-based training and assessment of technical and non-technical fundamental and advanced skills such as trauma care [5], airway management, and extracorporeal cardiopulmonary resuscitation [6,7]. Simulation is used to teach teamworking skills and delivery of care in an interprofessional setting [8]. The patient safety movement's epidemiologic data revealed targets for improving patient care and SBHE has been integrated into patient safety and quality improvement programs, with demonstrated improvement in patient outcomes [9].

Best practices for SBHE have been described in several domains, including debriefing, scenario design, faculty development, and educator skills [3,10-12]. Optimization of SBHE continues to evolve and requires recognition of validated educational outcome metrics [3]. When contrasted with traditional healthcare education methodologies, including didactic lectures and bedside teaching, SBHE can offer improved learning outcomes in some situations [2].

SBHE is a resource intensive technique compared to traditional established education methods. Increased resource requirements can be easily understood in terms of not only capital expenses for equipment and variable cost of supplies, but also in terms of educator to student ratios, physical space, and requirements for training of skilled simulation educators, instructional designers, and technicians. Efficiency is a function of the relationship between value of resources expended and the value of output, measured as educational effectiveness in the case of healthcare education and training. Quantitation of required SBHE resources is straightforward regarding equipment supplies and space but is more difficult to quantify with regard to time and resources required for the development of effective faculty skills for simulation instructional design, facilitation, and assessment of learners.

Metrics which reliably reflect educator skills and curricular design resulting in optimal educational outcomes remain an ongoing challenge in SBHE [13]. One example is educator debriefing skills which can be measured by validated tools such as the Debriefing Assessment for Simula-

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tion in Healthcare (DASH) and Objective Structured Assessment of Debriefing (OSAD) rubrics [14,15] for assessment of debriefing events and debriefer skills. These tools are incomplete in that they reliably rate a single debriefer's skills but have yet to be proven to correlate with improved learner outcomes.

## THE PRESENT: WE HAVE A LOT OF TOOLS

Advances in simulation have relied upon parallel progress in technology and educational design. Simulation technologies have become increasingly sophisticated, offering ever-more realistic representations. Realistic dynamic representations of physiology and anatomy in mannequins and task trainers present students with scenarios and training which are responsive to learner inputs, offering educators opportunity to observe and rate performance for both formative and summative purposes.

The potential for SBHE future applications depends upon thoughtful use of technological advances to support evidence-based instructional design principles. Demonstrated learning outcomes and ultimately clinical performance should guide development and integration of technologies for SBHE. High levels of realism and fidelity, originally thought to enhance learning, require careful design consideration, since the degree of realism does not always correlate with improved education outcomes, yet usually requires more resources than less realistic simulation [16,17]. Refinement and advances in instructional design, facilitation, assessment, and optimization of SBHE will assure efficient utilization and effective learning outcomes including valid competency assessment. An example of evidence-based design is the deliberate practice and mastery learning competency development and assessment strategy [18,19].

The combination of effective instructional methods and advanced technological developments offers a powerful synergy for creative applications of simulation to fill existing gaps in training and to address problem areas in the provision of clinical care such as patient safety. The Event-based Approach to Simulation-based Teamwork (EBAT) published in 2008 offers a structured approach to curriculum development which incorporates elements of current SBHE guidelines and teamwork training strategies [20]. Validation of rubrics such as EBAT and dissemination of accessible techniques to rapidly develop, assess, and implement targeted training outcomes is required to accelerate efficient and effective SBHE. Education outcomes research should be used to guide and accelerate the design of new simulators and simulation training rubrics. SBHE is a mature educational method, with both old and new implementation barriers such as individual, institutional, and academic resistance to change, unclear efficiency metrics, bud-

gets, faculty availability and training, and sustainability [12,21–23].

## THE FUTURE: BUILDING EVIDENCE-BASED EDUCATION

Breakthroughs in technology hold exceptional promise for mitigating SBHE implementation barriers and for improving efficiency and effectiveness. The scope of simulation technologies has expanded from physical task trainers and manikins with computer interfaces, to include immersive environments including computer augmented virtual environments and virtual reality (VR) headsets, and synchronous distance simulation [22,24–26]. Remarkable advances in simulators capable of representing increasingly realistic learner interactions during SBHE have outpaced advances in evidence-based educational processes to most effectively and efficiently employ simulation. SBHE educational paradigms, such as rapid cycle deliberate practice [27], virtual simulation [24], and simulation at a distance, must leverage the expanding portfolio of simulation devices and other SBHE enabling technologies to enhance healthcare learner outcomes and educational systems' effectiveness. Optimizing existing and future technologies including fully immersive environments using augmented reality (AR) and VR displays, interactions in the metaverse, airway haptics [28], and olfactory stimuli [17] will require research into many fundamentally unanswered questions regarding pedagogies, assessment, and outcomes. The Society for Simulation in Healthcare (SSH) recently established the top ten questions and priorities for healthcare simulation research, including uncovering best research designs to investigate simulation effectiveness, studying the dose response relationship between simulation training and patient care outcomes, effective approaches to patient safety, and the impact of learning strategies [13].

Advances in simulating reality have grown rapidly with multiple marketed devices and systems. Real-time synchronous learner interactions in roles represented by avatars are a technological achievement, yet this methodology like others has yet to find an optimal place in healthcare education and requires new paradigms, such as how to debrief an avatar or artificial intelligence (AI)-based interaction?

AI considerations for educational design reveal potential to significantly enhance SBHE [29,30]. AI algorithms for industries including finance, social media, advertising, and digital image design provide a jumpstart to guide SBHE applications. We can imagine that AI applications could be used to author scenarios with integrated key learning points, checklists, and other intelligent assessment tools. Facilitation and debriefing guides could be based upon not only evidence-based best practices, but on individual

learning curves. Automated design could integrate and control responsive real-time “on-the-fly” scenario modifications to support learner engagement, in the same way that current AI engines present players challenges in the world of online games.

Imagine, automated personalized learning! New pedagogical tactics for designing learning in an AI world will guide the future of educational design in many dimensions, including simulation. One such example is the application of AI using neural networks and real-time assessment of learner performance. AI could enable integration of sensor data from existing haptics based systems to easily provide real-time feedback based on individual learners' performance of complex and simple tasks, and application of knowledge in increasingly realistic simulation experiences. Real-time feedback is already available and effective in guiding learner performance in quality cardiopulmonary resuscitation, for both simulated training and actual clinical applications. AI systems could significantly enhance SBHE learning process' by providing greater precision and more accurate feedback, generating personalized training experiences.

I think the future of SBHE will focus on making teaching and learning more efficient. Improvements in instructional design, educator training, personalized learning experiences, and assessment will generate efficient learning curves, and valid competency assessments. Advances in educational methods and technologies will shift from parallel activities to aligned and integrated activities to enhance efficiency and accessibility of SBHE.

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# Data integration using information and communication technology for emergency medical services and systems

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Lack of resources is a challenging issue in emergency medicine. As a result, emergency medical systems and services (EMS) are being developed to overcome problems with limited emergency medical resources [1]. In particular, because it is difficult to provide high-quality emergency care outside of medical institutions, information between emergency medical centers and local communities must be connected efficiently [1-4].

The connections in the EMS can be discussed from two perspectives. First, for efficient emergency patient treatment and transportation based on medical guidance, the connection of information between the prehospital and hospital stages in the community must be performed in real time. Second, quality management should be performed based on large-scale integrated data between the two stages for the governance of EMS in the community.

Therefore, we can discuss the problems facing EMS in Korea from the perspective of information connections. The EMS policy in Korea, especially in the prehospital stage, is still dominated by consensus-based protocols rather than evidence-based protocols. This is because there is insufficient evidence to use an integrated dataset from the EMS [5]. The data management participants of the prehospital and hospital stages are different, and their information linkage is delayed for reasons such as the Personal Information Protection Act [6].

Various efforts have been made to derive scientific evidence on EMS issues by integrating large-scale data sources extracted from the community [7-10]. To integrate large-scale data sources, matching through key values is required; however, complete matching without missing values is difficult because of the heterogeneity of registries [6,11]. Even if it is possible to solve technical issues, integrating large-scale registries that include sensitive personal information (medical information) requires a latent period for administrative processes and approval from each authority. To overcome this delay, each authority needs a platform that can transmit the selected information from its registry in real time and collect it in a standardized format. Advances in 5G communications and clouding technology have enabled the use of these platforms in EMS [12].

Most datasets used in the EMS field are composed of structured data. Structured data are created in a tabular form through manual primary processing. Owing to limitations in physical space and time, it is difficult for providers to convert various events that occur in the EMS field into tabular data sources in real time. Accordingly, unstructured data that cannot be converted into a tabular form cannot be stored as a dataset, and the reliability of structured data cannot be guaranteed [11]. Therefore, the current dataset, which was manually collected in tabular form, did not fully reflect the EMS event (Fig. 1).

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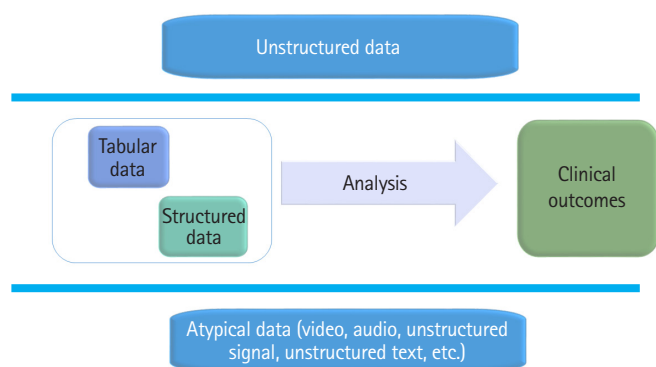


Fig. 1. Emergency medical services and systems data and evidence flow.

The development of digital health technology makes it possible to collect information in an atypical form that is currently disappearing in the EMS field [13,14]. There are several studies in which unstructured data such as voice, vital signals, and video information are collected through wearable devices and 5G networks to derive evidence in emergency medicine. They showed that a technology capable of collecting unstructured data in real time in the field of emergency medicine could improve clinical practice [15–17]. In the future, the development of unstructured data collection and processing capacity can enhance first aid capacity by analyzing information that is not available in the EMS field in real time and can contribute to quality management from high-quality datasets [12,18,19].

The development of information and communication technology enables the rapid sharing of diverse and vast information generated from the EMS field and facilitates the data integration of each entity. This improves the quality of management provided at the prehospital stage and helps derive high-quality evidence that reflects the reality of the local community. However, information based on relevant legal and institutional arrangements and social implications is supported. Therefore, in the future, efforts to complete regionalization by establishing a data-driven precision EMS centering on the local community should continue.

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# Current challenges in adopting machine learning to critical care and emergency medicine

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Over the past decades, the field of machine learning (ML) has made great strides in medicine. Despite the number of ML-inspired publications in the clinical arena, the results and implications are not readily accepted at the bedside. Although ML is very powerful in deciphering hidden patterns in complex critical care and emergency medicine data, various factors including data, feature generation, model design, performance assessment, and limited implementation could affect the utility of the research. In this short review, a series of current challenges of adopting ML models to clinical research will be discussed.

**Keywords** Machine learning; Challenges; Artificial intelligence; Critical care

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## Capsule Summary

### What is already known

*Machine learning is a powerful tool to handle complex datasets and could serve as a promising research methodology to improve healthcare outcomes in critical care and emergency medicine.*

### What is new in the current study

*Various challenges and pitfalls should be considered in conducting clinical research using machine learning.*

## INTRODUCTION

Over the past decades, the field of machine learning (ML) has made great strides in medicine. The greater availability of large datasets—supported by lower data storage fees and the advent of cloud computing—has provided a rich source of information that can be mined for ML algorithms [1]. Furthermore, enhanced computing power has accelerated the development of ML algorithms that can process complex, heterogeneous datasets involving imaging data, electronic health records, and waveforms [2]. The dramatic evolution of ML techniques has inspired researchers to build numerous prototype models for prediction, diagnosis, and prognostication. A number of these models performed equal or better in prediction and diagnosis than existing conventional statistics-based solutions. Various ML models, for example, predicted critical care outcomes—e.g., emergency department (ED) to intensive care unit (ICU) transfer and in-hospital mortality—more accurately than existing screening tools, such as the Modified Early Warning Score, the National Early Warning Score, and the Sequential Organ Failure Assessment [3,4]. In radiology, ML-based radiomics models performed better than radiologists, especially in detecting subtle changes indescribable to the naked eye [5–7].

Nonetheless, several challenges must be overcome before ML algorithms can be adapted to the clinical workflow of the ICU or ED (Fig. 1). In this review, we outline these challenges—both in developing and applying models for critical care medicine—and offer potential solutions.

## CRITICAL CARE DATA

The extensive and granular datasets available in critical care medicine are promising resources for developing ML models. It is especially true when the data contain a lot of noise from the envi-

ronment, such as raw vital sign data acquired from the ED. However, several challenges remain in data standardization and preprocessing.

Building a reliable ML model requires a highly structured, large, and multicenter dataset that allows for proper model training as well as internal and external validation. But obtaining such a dataset is no easy task. Electronic health records contain information collected as part of the workflow and are thus fraught with errors such as mislabeling and omission, and variation in intra-hospital and interhospital reporting of clinical data creates additional challenges in data mining.

Thankfully, a number of efforts are underway to standardize data formatting. For example, Fast Healthcare Interoperability Resources (FHIR) is a preformatted healthcare database that analytics platforms can easily access and deconstruct [8]. More recently, the Critical Care Data Exchange Format (CCDEF) was developed to facilitate encoding, storing, and exchanging clinical and physiologic data across institutions globally [9]. CCDEF generates a diverse and well-represented dataset that is ideal for developing robust ML algorithms.

Once data has been gathered, optimizing the dataset through preprocessing is necessary before being employed in an ML model. Preprocessing can involve data cleaning, normalization, feature extraction, and selection to address issues with erroneous, missing, or imprecise data. Proper data preprocessing requires tremendous resources and time due to considerable size of datasets containing physiological and imaging data and directly influences the performance of the ML algorithm [10,11]. Nonetheless, the omission of preprocessing in ML studies appears common and impairs a fair assessment of the model. Even with proper preprocessing, features that may be difficult to capture in data, such as heart rate variability and interhospital differences in ICU resources, can still confound the model performance [12,13].

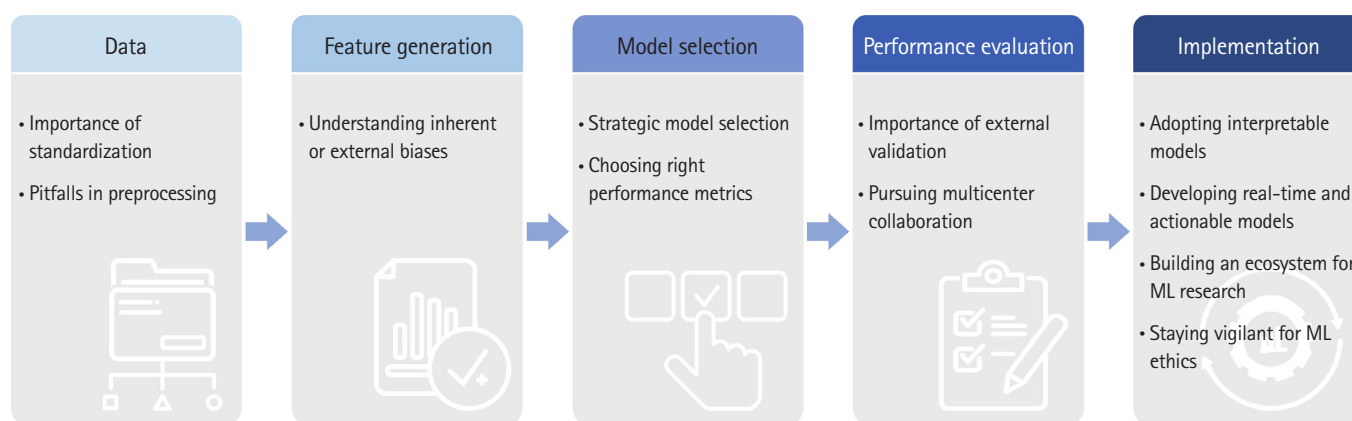


Fig. 1. Challenges in adopting machine learning (ML).

## FEATURIZATION AND MODEL SELECTION

Featurization involves converting raw variables into numerical vectors that ML algorithms can process. Feature selection and extraction are important steps to identify clinically salient features and improve model predictability [14,15]. Therefore, features need to reflect underlying pathophysiologic mechanisms or core characteristics of data structure. For feature extraction, one needs to understand inherent biases in feature extraction (measurement error, self-reporting, human judgment) which can lead to the problem of fairness in ML. When choosing the models, they need to be built on the same well-understood variables to fairly compare their performance. Likewise, careful contextual consideration needs to be given when choosing the ML model. Another potential problem is using various ML models without consideration of data structure and study objectives, including simultaneous use of supervised and unsupervised learning just to see better performance for publication.

## EVALUATION OF ML MODELS

Once the features are decided, models learn from the selected features within the different hyperparameter settings to predict desired outcomes. Choosing the best model requires calibration, which estimates concordance between the predicted probabilities and observed outcomes. Model calibration is a necessary step for measuring the relative performance of models and can assess underfitting or overfitting [16]. To evaluate fair model selection, future studies should use appropriate methods of model calibration, accounting for population size and the type of model [17]. Finally, the evaluation of a model's predictive performance should assess its clinical applicability. Most of the existing studies have used the area under the receiver operating characteristics (AUROC) curve to evaluate model performance. The AUROC curve is plotted by calculating sensitivity and specificity at different thresholds. An AUROC curve provides a single performance value that is easy to interpret and compare [18]. Because the AUROC curve accounts for the true positive rate and the false positive rate, it is useful in a balanced dataset that values both positive and negative outcomes equally. The existing ML studies use the AUROC curve indiscriminately. However, the datasets used to build ML models in medicine tend to have smaller positive classes compared to negative classes. In such imbalanced datasets, the area under the precision recall curve (AUPRC) is more appropriate. The AUPRC represents positive predictive values for each true positive rate and thus focuses on positive values and is not influenced by true negatives [19]. Therefore, the use of AUPRC to evaluate mod-

els used for problems such as diagnosis, screening, and predicting mortality will lead to better estimation of the models' performance in real clinical settings.

## MODEL VALIDATION

Although ML models are being rapidly developed for potential use in critical care medicine, their clinical utility is still unclear with a lack of generalizability. Small datasets, especially those produced from a single institution could lead to overfitting in a similar environment, but often not performing in other datasets. To properly implement ML algorithms in the clinical workflow of the ICU or ED, the algorithms must be externally validated. However, a recent study assessing the clinical readiness of existing ML models revealed that only 5% of the models have been externally validated [20]. Ongoing data-standardization initiatives, such as CCDEF, will hopefully integrate large datasets across multiple centers, which in turn can be employed for model validation. Further, successful model performance on prospectively collected data can demonstrate the value of ML support in clinical settings and assure clinicians of its safety.

Lack of external validation and small datasets can lead to overfitting and reduce generalizability. While curating multicenter databases in a centralized center can resolve such issues, it invites other challenges, especially in international configurations due to concerns over privacy, technical process, and data ownership. Federated learning (FL) provides a more efficient solution by allowing multiple collaborators to train models in parallel and send the updates to a central server to be integrated into a consensus model [21]. Recently, 20 centers across the globe collaborated to build a comprehensive FL model for predicting outcomes from COVID-19 infection [22]. Trained on electronic medical records and chest x-ray images, the FL model performed 16% better than a locally-trained model in predicting 24-hour oxygen treatment, with improved generalizability of 25.3%. As above, data sharing in a federated environment could overcome the limitation of external validation where data governance and privacy become obstacles.

## MODEL IMPLEMENTATION

Despite a great deal of evolution in ML, several challenges still remain before their deployment. When the models are deployed at the bedside to alert physicians of impending crises, for example, their overt sensitivity can cause unintended harm. Excessive alarms that do not require clinicians' immediate awareness can lead to missed real events. The ML-based alerting tools should be

designed in a judicious manner to maximize the accuracy of the alarms.

Although not required, model interpretability could have a paramount impact on successful implementation. To implement a model in a clinical setting, its decisions must be verified by clinicians before use. An earlier study tested ML algorithms to build a model that could triage patients with pneumonia and predict mortality. Among the algorithms evaluated in the study, multitask neural networks were deemed to be the most accurate [23]. However, later analysis revealed a pattern in the algorithm that linked asthma to lower mortality—explained by the fact that patients with asthma received more attentive care and close monitoring, thus leading to better outcomes.

Since the study was published, efforts have been made to improve the interpretability of ML models. Prescience, a complex ML algorithm, accurately predicts the near-term risk of hypoxemia during surgery and displays the specific risk factors that informed its prediction [24]. The model is built using a gradient boosting machine based on both static features—such as body mass index, age, and sex—and dynamic parametric values, such as tidal volume and vital signs. The impact of each feature is assigned Sharply values, which makes the predictions more interpretable through the concept used in the game theory.

The successful implementation of ML models relies on clinicians' confidence in the models, which depends on how well users can explain the models' decision-making process [25]. For an ML model to play a supportive role to physicians, it is paramount to focus on features that are available real time and actionable in clinical settings. Therefore, researchers and developers should involve clinicians in an early phase of design to facilitate smooth integration into clinical workflow [26,27].

As seen from the above examples, the ML model implementation in ICU or ED population still could be far-fetched from the practice pattern of clinicians. To address that aspect from the end-user standpoint, the US Food and Drug Administration (FDA) under the Department of Health and Human Services has published an action plan for the use of artificial intelligence and ML, specifically in the form of "Software as a Medical Device (SaMD)." In the white paper, the FDA argued the need for the "Predetermined Change Control Plan" to assure the quality of usable ML models for patient care [28]. Similar efforts could be seen in the Bridge2AI, a US National Institutes of Health funding initiative to promote the ML modeling environment at a multicenter level [29]. Filling the gap between the developer's machine to the real world remains to be a huge challenge for healthcare researchers.

Lastly, For the ML model to be successfully implemented at the bedside and performed in the realm of current clinical practice,

not only the ML researchers but also clinicians (end-users) need to understand the ethical aspects of adopting it. First, all data and system-related biases should be minimized with vigilance. Bias could include a thorough examination of the environment where the model was initially developed, identification of inadequate perpetuation of systematic errors abundant in different types of healthcare practices, and so on [30]. Secondly, both researchers and clinicians need to recognize that patients and colleagues might not accept or adhere to the results of the ML model. In a survey, around 60% of Americans feel uncomfortable using artificial intelligence-driven healthcare and are also suspicious that the ML model could improve their outcomes [31]. More studies are required to understand the underlying characteristics of barriers to accepting ML in practice. Thirdly, clinicians still should strive for excellence in patient care in their traditional ways. This due diligence is mainly to avoid the moral hazards smoldering when high-performing ML models become functional at the bedside.

## CONCLUSION

Research in the application of ML to critical care or emergency medicine has seen tremendous growth owing to the increasing availability of highly granular, large critical care databases. Nevertheless, for the ML-based models to serve as reliable decision support tools, the steps involved in model building to final implementation must be carefully examined. As the validity of the models is entirely dependent on the datasets, standardization of the data-gathering process and proper preprocessing of the datasets are imperative. A large portion of published studies lack a description of the preprocessing and featurization bringing into question the clinical saliency of the features involved in model performance. Moreover, selecting the right model should involve model calibration to objectively compare the accuracy of the model prediction. Even after choosing the well-calibrated model, many of the earlier studies failed to have the models externally validated which may result in the models overfitting the testing dataset reducing generalizability. In addition, the decision-making process of the algorithms should be explainable. Lastly, the endeavor to create a sustainable and scalable ecosystem should be pursued across different healthcare systems where ethical datasets could be collected and shared for fair ML research.

## ETHICS STATEMENTS

Not applicable.

## CONFLICT OF INTEREST

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

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## AUTHOR CONTRIBUTIONS

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# To resuscitate or not to resuscitate? The crossroads of ethical decision- making in resuscitation in the emergency department

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Emergency physicians (EPs) working in low-resource settings, where patients mainly bear the cost of healthcare delivery, face many challenges. Emergency care is patient-centered and ethical challenges are numerous in situations where patient autonomy and beneficence are fragile. This review discusses some of the common bioethical issues in the resuscitation and postresuscitation phases of treatment. Solutions are proposed and the necessity for evidence-based ethics and unanimity on ethical standards is emphasized. After a consensus was reached on the structure of the article, smaller groups of authors (2–3) wrote narrative reviews of ethical issues such as patient autonomy and honesty, beneficence and nonmaleficence, dignity, justice, and specific practices and circumstances such as family presence during resuscitation after discussions with senior EPs. Ethical dilemmas were discussed, and solutions were proposed. Cases related to medical decision-making by proxy, financial constraints in management, and resuscitation in the face of medical futility have been discussed. Solutions proposed include the early-stage involvement of hospital ethics committees, financial assurance in place beforehand, and allowing some leverage on a case-to-case basis when care is futile. We recommend developing evidence-based national ethical guidelines and incorporating societal and cultural norms with autonomy, beneficence, nonmaleficence, honesty, and justice principles.

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## Capsule Summary

### What is already known

*Decision-making on the resuscitation of critically ill patients is a challenging task worldwide. Globally there are ethical guidelines that assist emergency physicians in decision-making on the resuscitation of such patients. However, emergency physicians still face difficulties in decision-making.*

### What is new in the current study

*This narrative review reflects on how different and difficult the decision-making process is in resource-limited settings. No large-scale studies exist to explore the factors, barriers, problems, and perspectives behind decision-making in resource-limited settings. Perhaps, having a set of clear ethical guidelines to follow would be the best solution for the emergency physician in a resource-limited setting.*

## INTRODUCTION

Resuscitation is derived from a Latin word that means "to set in motion." Resuscitation traditionally encompasses a variety of interventions such as intravenous fluids, oxygen, vasopressors or inotropes, antibiotics, and cardiopulmonary resuscitation (CPR) [1]. The goals of resuscitation are like other medical interventions: to save a life, restore health, relieve distress, and limit disability [2]. Unlike other resuscitative interventions, CPR is unique: it can reverse the loss of life— a clinical outcome achieved by only a few who experience in-hospital cardiac arrest and even fewer who experience out-of-hospital cardiac arrest [3–6]. Procedures for when to initiate or to stop resuscitative efforts vary globally and depend on several factors: the clinical condition of the patient, comorbid conditions, cultural and religious beliefs, social expectations, the guardian's perception of the patient's condition, moral principles, anticipated clinical outcome and, occasionally, the patient's autonomy, preference, or advanced directive [2].

In the past three decades, resuscitation science has progressed remarkably with advancements in CPR techniques. Different resuscitation councils have devised guidelines to standardize resuscitation of patients with cardiac arrest or critically ill patients who might develop cardiac arrest. However, reflex initiation of CPR or resuscitative efforts has faced criticism [7]. There are two schools of thought in this regard. First, resuscitation efforts should be attempted for any patient who has at least a theoretical chance of survival [8]. Second, resuscitation efforts should be attempted only if there is a realistic likelihood of benefit to the patient based on existing scientific evidence and reasonable medical judgment [9,10]. The antithesis of the first view is that it might require many resources that could be better used elsewhere and divert practice from outcome-based resuscitation to universal resuscitation instead [2]. This plays a major role in resource-limited settings where the unreasonable use of resources could hypothetically cost a life that could be saved [11]. The antithesis of the second view is that it involves human factors that are complex to mea-

sure in real-life cardiac arrest scenarios and are not currently accounted for in existing resuscitation guidelines [12,13]. For example, the views of two physicians of the same level can differ on the initiation or termination of resuscitation of the same patient. The interpretation of a situation might be influenced by the scientific, religious, metaphysical, and socioeconomical background of the individual.

Therefore, decision-making in resuscitation is intricate and error-prone even in developed countries. In 2012, The National Confidential Enquiry into Patient Outcome and Death (NCEPOD) report noted frequent failures to consider resuscitation status, a high number of futile resuscitation attempts in frail patients with substantial comorbidities, limited engagement of families and patients in reaching do not attempt-CPR decisions, and 43% of cases in which CPR was performed against the expressed will of the patients [14].

On the other hand, in the resource-limited settings of low- and middle-income countries, the situation is a dilemma as there have been no studies to determine objectively the practice of decision-making in resuscitation and the beliefs surrounding it. However, low literacy rates, poverty, extreme religious beliefs, regressive social values, extended family structure, and low socioeconomic conditions might add to the complexity of the decision-making process in resuscitation.

The decision to initiate or terminate resuscitative efforts rests with the physician dealing with the patient. The physician should use the available information about the patient's premorbid conditions, time unresponsive or in a state of cardiac arrest, acute illness, and the trajectory of resuscitation. Differences in ethical and cultural norms should be the last thing to be considered by the physician while deciding when to initiate or terminate resuscitative efforts. Although the common principles of autonomy, beneficence, nonmaleficence, and justice (Table 1) appear to be accepted across different cultures, the priority of these principles may vary among different cultures. Physicians should play a role in decision-making regarding resuscitation based on scientific

**Table 1.** Definition of ethical principles that come into consideration during resuscitation

Ethical principle	Definition
Autonomy	The principle of respect for patient autonomy. Physicians do not have the right to treat patients without their consent or in Latin " <i>voluntas aegroti suprema lex est.</i> "
Beneficence	The principle of beneficence means the provision of benefits as the promotion of welfare. Beneficence requires positive steps to help others. In Latin, " <i>bonum facere</i> " or " <i>salus aegroti suprema lex est.</i> "
Nonmaleficence	The principle "above all do not harm," or in Latin " <i>primum non nocere.</i> " Nonmaleficence involves obligation not to inflict harm on others.
Justice	The principle of justice affects priorities in the allocation of healthcare resources. Justice may be defined as giving each person which is due, and which can be claimed legitimately.
Honesty	Honesty is defined as "fairness and straightforwardness of conduct" or "adherence to the facts."
Dignity	Dignity is defined as "a state, inherent respect, worthy of honor, or high regard."

**Table 2.** Common ethical challenges observed in the resuscitation room and associated principles of bioethics

Ethical challenges during resuscitation	Ethics principle
Needing central venous access for ionotropic initiation	Beneficence and nonmaleficence vs. autonomy and dignity
Decision for CPR	Beneficence and nonmaleficence vs. autonomy and dignity
Decision to intubate	Beneficence and nonmaleficence vs. autonomy and dignity
Discontinuation of CPR	Nonmaleficence and dignity
Continuation of life-sustaining treatment as per demographic and clinical features	Beneficence and nonmaleficence
Family involvement in decision-making during resuscitation	Honesty, autonomy, beneficence and nonmaleficence, dignity, and justice
Patient accessibility to best quality care	Justice
Transfer of patients to other hospitals due to financial constraints	Justice

CPR, cardiopulmonary resuscitation.

evidence and resuscitation guidelines [2]. In this narrative review, we discuss the real-life ethical issues of resuscitation in low- and middle-income countries (Table 2) and review of the literature to provide ethical solutions to these problems.

## METHODOLOGY

This review article explores the ethical dilemmas that are commonly encountered by emergency physicians (EPs) in the emergency department (ED) of a low- and middle-income country through the concept of basic ethical principles. The selection of cases was based on a discussion among the core team, which included EPs (residents and consultants). The cases are those that are commonly encountered and were selected following a review by an independent emergency physician not included in the core team. Each case was assessed using the basic ethical principles described in Table 1. The conclusion of each case reached a consensus through feedback from each core team member.

## ETHICAL CHALLENGES DURING RESUSCITATION

### Case 1: the right to refuse

A 69-year-old female patient with a prior history of asthma attended the ED with complaints of fever for 7 days and shortness of breath for 4 days. Upon arrival, the patient was in impending respiratory failure with a silent chest. The diagnosis of life-threatening asthma was made. Initial treatment was initiated and the patient's next-of-kin, her daughters, were counseled regarding the need for emergent intubation and invasive mechanical ventilation. The daughters refused this intervention despite being counseled by a team consisting of pulmonologists, intensivists, and EPs. Their refusal was centered on the fact that the patient had attended an ED with acute asthma exacerbation multiple times, and her management precluded this intervention each time. Why should this time be any different? The patient was deemed not to have the capacity to dis-

cuss the decision, as she was in severe respiratory distress, suffering hypoxic respiratory failure, and was hemodynamically unstable. There were no other surrogates. The patient eventually succumbed to her illness and expired in the ED.

### Ethical challenges and resolution

A clear distinction between competence and capacity already exists in the literature. Competence is a legal term whereas capacity is a medical one. Competence refers to the mental ability of a person to participate in or execute legally recognized activities such as preparing a will, standing trial, entering a legally binding contract, and making medical decisions. To declare a person incompetent is a judicial decision. Capacity, on the other hand, is determined by a physician [15]. This is done when we explain a part or the whole of the management plan to the patient. The patient is assessed on their ability to understand the information, retain the information, weigh all the pros and cons, and then come to a rational conclusion and communicate it by any means necessary. Any patient found to be lacking capacity is *de facto* incompetent, and as such a legal verdict is not needed. These patients cannot exercise their right to choose or refuse treatment, so either the treating physician or a *de facto* surrogate decision-maker must act on their behalf [16]. There are several loopholes to this, and the entire process is not as straightforward as it may seem on paper. It is important to understand that capacity can fluctuate, and a patient may be capable of making one decision but not another. The more critical the decision, the more formal should be the assessment [17]. There are several tools available for capacity assessment and these include the Mini-Mental State Examination, Montreal Cognitive Assessment, Hopkins Competency Assessment, MacArthur Competency Tool for Assessment for Treatment, Competency Interview Schedule, and Structured Interview for Competency [18,19]. The capacity assessment followed unanimously in the institution should be used by the physician and in complex cases, the findings can be corroborated between colleagues and then documented. Psychiatric consultation

may be prudent in some clinical settings where mental health conditions such as schizophrenia might be interfering with the capacity of the individual to decide.

The first step is always a thorough assessment of a patient's capacity before the involvement of surrogate decision-makers. Once a patient's lack of capacity is established, the next important question is who gets to decide on behalf of the patient. Ideally, it should be someone chosen previously by the patient. This may include a primary care physician, an attorney, or the next-of-kin. Their decisions should be based on the moral values and personal beliefs of the patient. The core concepts of beneficence and nonmaleficence must be applied and followed by everyone at the bedside of the patient, be it their physician, their nursing staff, or their surrogate. Three problems can be encountered here. First, what if there is no surrogate? In cases when no surrogate is available, and the patient requires emergent care, then the physician might administer life-sustaining treatments as per institutional protocols. This is consistent with the four ethical principles that govern physician conduct: autonomy, beneficence, nonmaleficence, and justice. Second, what if the physician wishes to override the decision of the designated medical proxy? This is a uniquely challenging scenario with potentially more than one viable solution. This can only be supported by the institution if a consensus between the different treating physicians determines that the designated medical proxy is not acting in the best interests of the patient. The ideas and concerns of the designated medical proxy should be explored at length before such a consensus is reached. The institutional ethical review committee, if present and functional, should be involved early on to avoid liabilities. Third, if the patient has discussed their wishes in advance, it is important to honor those wishes as closely as possible. However, if there is no documentation of the patient's wishes, the surrogate decision-maker should be careful not to make decisions based solely on their values and beliefs, as this may not align with the prior intentions of the patient. Many organizations and nations have protocols in place for this process, and it is important to follow these protocols to ensure that the wishes of the patient are respected. However, no such guideline or protocol exists in the healthcare system of Pakistan to safeguard the end-of-life or life-sustaining decisions made by the patient before losing decision-making capacity. Subsequently, it lies with the surrogate to decide on their behalf regardless. This warrants the development of a protocol or policy addressing this issue on a national level.

In the above scenario, it was established early on that the patient lacked capacity. It was also ascertained that the patient had not appointed any medical proxy. Therefore, the next-of-kin present (her daughters) was included in the decision-making process.

It was here that a controversy arose. The treating physician believed that the decision by the next-of-kin was not in the best interest of the patient. While their intentions were not malevolent and stemmed from a lack of understanding of the disease and unfounded fear of "putting patients on the vent," asthma is a reversible condition and the family's refusal to allow intubation possibly caused her death. A resolution to this could have been achieved by involving the hospital ethics committee earlier in the process.

### Case 2: is money everything?

A 23-year-old female patient with no known prior comorbid conditions came to the ED just beyond the 4.5-hour window with sudden onset right-sided motor weakness and aphasia. Her National Institutes Health Stroke Scale (NIHSS) at presentation was 17. The neurology team was brought on board. Computed tomography (CT) of the head and CT angiogram of the internal carotid arteries (ICAs) were done and demonstrated a large thrombus occluding the left ICA with a subtle filling defect of the left middle cerebral artery collaterals. Intra-arterial thrombolysis was planned by the interventional radiology team, which is a costly procedure. The patient's family had financial constraints and refused this treatment, knowing that the outcome of the young previously healthy patient might be adversely affected. The physicians and the family understood that the patient might not be able to speak or move as she had previously. The family eventually decided to move the patient to a government hospital where interventional radiology expertise was not available.

### Ethical challenges and resolution

Let this discussion begin with a little perspective: after the landmark 1986 passage of the Emergency Medical Treatment and Labor Act (EMTALA), the emergency care of patients in the United States was revolutionized [20]. There are three basic provisions for hospital and emergency medical services (EMS) as per EMTALA. First, any patient presenting to a hospital ED must undergo an "appropriate" medical screening examination by qualified medical personnel to determine if they have an "emergency medical condition." Second, patients who have an "emergency medical condition" must be "stabilized" within the capabilities of the facility. If definite treatment is not available, then the patient should be timely moved to another facility with the required capabilities, only after "stabilization." Third, if the patient with the "emergency medical condition" cannot be "stabilized," they can be moved to another facility only if the physician decides that the benefits of treatment far outweigh the risks of unsafe transfer. Hospitals in the United States are mandated by the EMTALA to accept Medi-

care funding. EDs are required by law to follow all these three provisions regardless of the ability or inability of the patient to pay for their emergency care [21,22]. In their policy statement titled Code of Ethics for EPs, the American College of Emergency Physicians (ACEP) reaffirms that EPs shall respond promptly and expertly, without prejudice or partiality, to the need for emergency medical care [23]. The ethical principle of justice means the quality and level of emergency care should not be dictated by the financial capabilities of the patient.

This is a shared responsibility of the EPs and society at large to ensure that there is sensible resource allocation such that the medical benefits and financial burdens of each patient should be balanced against each other [24–27]. This means that the EP plays a central role in deciding when to limit treatments if the cost outweighs the cure [28]. The country must invest in a robust emergency care infrastructure consisting of EMS, hospitals, and relevant healthcare policies. Emergency care should be widely available (especially in the remote areas of Pakistan), easily accessible (patients should safely reach definitive care), and universally acceptable (the quality and level of emergency care should be maintained in both public and private sectors). The obligation to provide resources for emergency care should lie either with a governmental health service or single-payer insurance. A distinction between patients requiring emergent and nonemergent care should be made in the context of limited resources so that only the subset of patients in the former category can be accommodated by the ED. In short, in the unique case that we have highlighted, patient management would not have been compromised if the provision of care in a low- and middle-income country like Pakistan was to a standard that it should be, affordable, and equal for all.

However, while this is the ideal scenario, ground realities are what the EP must face every day. What options do they have on an individual level and how can emergency care be strengthened at an institutional level to prevent such patients from falling through the net? Individually, the physician can determine if any charity is available. If not, then they will either lower the standard of care, refer the patient to a safety net provider (as was done in this case), reduce their fees, or force the patient to go into debt. Although whatever options can be exercised in the short term should be used, it is unsustainable to do so over a long period. Therefore, addressing patient financial concerns should be done at an institutional level. Some options include ensuring the financial status early in the treatment process so that arrangements can be made before embarking on a long route of expensive investigations and treatment. The hospital can make a list of lifesaving procedures that come under "stabilization" as outlined by EMTALA that will be covered by a built-in financial mechanism. Having a system in

place, no matter how minimalistic, ensures that the ethical burden is removed from the shoulders of the physician and placed on those of the institution [29].

### Case 3: what does futility mean to bereaved parents?

A 17-year-old boy with no prior known comorbid conditions was brought to the ED by his parents with complaints of fever for 4 days and altered sensorium for 1 day. The patient was hemodynamically unstable with a Glasgow Coma Scale score of 3 out of 15 upon arrival. He was intubated in the resuscitation room. He was diagnosed with septic shock, acute kidney injury, acute liver failure, disseminated intravascular coagulopathy, and acute myocardial injury. He remained hemodynamically unstable despite the use of dual vasopressors and an inotrope. He was moved immediately for head CT, which demonstrated diffuse cerebral edema and tonsillar herniation. The parents were counseled about their son's prognosis by intensivists and EPs, but they still had high hopes for his revival. The patient went into cardiopulmonary arrest in the ED. CPR was initiated as per advanced cardiac life support (ACLS) guidelines and carried out for 20 minutes. The parents were counseled regarding physiologic futility, but they insisted on continued resuscitative efforts. No return of spontaneous circulation was achieved, and the death of the patient was subsequently declared to the family.

### Ethical challenges and resolution

DNR has been a source of great controversy across the world. A DNR code status theoretically means that in the event of a cardiopulmonary arrest, no CPR as described in the ACLS guidelines should be attempted [30]. Maintaining the principles of autonomy, this decision solely lies with the patient unless they are either incapacitated or underage, in which case, the patient's surrogate will decide in their place [31,32]. The problem with obtaining code status in the ED is obvious: both time and information have limits that the EPs cannot overcome. This often creates a conflict between physicians and families: withholding CPR in cardiopulmonary arrest is misinterpreted as withholding other treatments and interventions. Families see it as physicians giving up on their patients. In 1988 Jennett [33] distinguished three reasons why CPR might be withheld: "CPR would be futile because it is very unlikely to be successful, the quality of life after CPR is likely to be changed to so poor a level as to be a greater burden than the benefit gained from the prolongation of life, and the quality of life is already so poor due to chronic or terminal disease that life should not be prolonged by CPR." This remains to be one of the most relevant descriptions, even today. Several acronyms are currently in use to inform the physician and nursing staff of a pa-

patient's resuscitation status, such as DNR, DNI (do not intubate), DNAR (do not attempt resuscitation), AND (allow natural death), etc. [34]. Choice of language is important. A simple "no CPR" would be more useful than other confusing options. It should be clearly stated in the medical records of the patient that only in the event of pulselessness and apnea, no CPR as per ACLS guidelines will be initiated. There should be no confusion among the physicians and staff that all other life-sustaining therapies up till the point of CPR will be provided.

How can physicians better communicate the concept of futility? "Preserving life at all costs" is often paid with the price of compromising a patient's dignity [35–43]. In deciding a management plan, physicians must consider the patient's objectives in seeking treatment as well as their objectives in administering that treatment. Quantitative futility refers to the unlikely chance that a proposed intervention will benefit the patient. Qualitative futility is when the proposed intervention, if successful, will probably produce such a poor outcome that it is deemed best not to attempt it. In simple terms, quantitative futility implies that the treatment is not going to work while qualitative futility indicates that the goal itself is undesirable. In complex cases such as the one mentioned above, it is best to avoid all this unnecessary medical jargon. To ensure clarity and build rapport, culturally appropriate terms should be used instead.

A compassion exception to accommodate the wishes of two grieving parents to see their dying son live a few hours longer, knowing his imminent death, can go a long way in easing their suffering. There are a lot of gray areas when it comes to life and death and physicians should decide on a case-by-case basis.

#### Case 4: God forbids it

A 36-year-old woman was brought in by her nephew with complaints of black stools and bloody vomiting for 3 days. She had a history of chronic use of nonsteroidal anti-inflammatory drugs for her knee pain. Upon arrival at the ED, the patient was found to be hemodynamically unstable. The gastroenterology team was brought on board and an emergent endoscopy was planned. Blood products were timely arranged and just as the on-call resident went to obtain the patient's consent, she refused. The patient explained that she was a Jehovah's Witness and that the transfusion of blood products was forbidden in her religion. This led to a great tumult in the resuscitation room. EPs and gastroenterologists spent the better part of the afternoon trying to convince the patient that her life was in imminent danger if she did not give consent. Jehovah's Witnesses are a religious minority in Pakistan. Statistically, most of us will spend our entire lives without encountering even one of them. The family eventually got fed up with

the aggressive attitude of the doctors and took the patient to another hospital.

#### Ethical challenges and resolution

Most of the ethical dilemmas we encounter during our medical careers can be examined in the context of the four basic principles of medical ethics defined by Beauchamp and Childress [44]: respect for autonomy, beneficence, nonmaleficence, and justice. Physicians should always respect their autonomy when deciding on a management plan for their patients [45–47]. This means they should accept the informed decisions of their patients, even when they refuse recommended treatment. To give informed consent, certain conditions should be met: the patients must retain the capacity to decide, and they should be able to understand the nature of the proposed procedure, along with its risks, benefits, suitable alternatives, and likely outcomes. There should be no hint of coercion on the part of the treating physician [48,49]. The patient must not feel threatened, bullied, or subjected to irresistible pressure to accept a decision that under normal circumstances they would not make. Should we as EPs uphold the rights of adult patients who refuse a particular intervention based on religious beliefs, even when such an intervention would be lifesaving? This is a challenging situation, indeed.

In this case, we should have ensured that the patient understood all the risks and benefits associated with accepting a blood transfusion. This includes the common risks of blood incompatibility, allergic reactions, transmission of bloodborne diseases, and volume overload. Did we communicate to her without coercion that a transfusion would improve her hemodynamic parameters? The patient's state of acute blood loss meant that there were no viable alternatives that we could offer her. The patient and her family should have been given a safe space to decide, knowing that the team of doctors would not abandon them in their time of need. They should not be ridiculed or seen as social outcasts just because they do not belong to a mainstream religion. Discussing the outcomes of the patient with her family would have made them come up with more viable solutions. There are several precedents in the medical literature concerning this ethical dilemma that the treating physicians could have used to help the patient and her family make a better-informed decision [50,51].

#### MOVING FORWARD

Throughout the article, a recurrent theme in the solutions to the ethical challenges presented is the need for the strengthening of the institution. This can be achieved with the internal ethical committee of the hospital or the health regulations of the gov-

ernment. What is important is that a set of guidelines be developed based on the principles of autonomy, beneficence, non-maleficence, honesty, and justice while incorporating cultural and societal factors as well, such as the EMTALA in the United States. Governments of low- and middle-income countries can then include the enforcement of these guidelines as part of the accreditation process for healthcare facilities. To promulgate these national standards further and bring them into daily usage in healthcare facilities, they should be included in medical curricula in both physician and nursing schools. This would ensure that all healthcare professionals are aware of the rights of their patients and how best to safeguard them in a wide variety of scenarios.

## CONCLUSION

Ethical issues are faced by EPs daily. However, due to the chaotic nature of the ED and the cognitive burden on EPs, physicians may not be able to make the most ethical decisions for their patients. Therefore, having a set of clear ethics guidelines by which the physician can abide would be the best solution for the emergency medicine practitioner.

## ETHICS STATEMENTS

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closed-circuit autotransfusion system in Jehovahs Witnesses patient. Masui 2000;49:1398–400.

# A clinical approach to an unidentified aerosolized bioterrorism agent: a narrative review for emergency providers

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The current heightened international political climate is accompanied by increased risk of chemical or biological agent weaponization. Historical accounts of biochemical warfare are extensive, and considering the recent use of such agents for targeted attacks, clinicians need to recognize and manage these cases. However, agent properties such as the color, odor, ability to be aerosolized, and long incubation period can introduce difficulties in the diagnostic and management approach. We searched PubMed and Scopus for a colorless, odorless, aerosolized substance with an incubation period of at least 4 hours. Data from articles were summarized and reported by agent. Based on data from the available literature, we included agents such as nerve agents, ricin, botulinum toxin, anthrax, tularemia, and psittacosis in this review. We also highlighted potential chemical and biological agents that could be weaponized and the optimal strategies for the diagnosis and treatment of patients exposed to an unknown aerosolized biological or chemical bioterrorism agent.

**Keywords** Chemical warfare agents; Biological warfare agents; Nerve agents; Bioterrorism; Emergency department

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## Capsule Summary

### What is already known

*Historical accounts of biochemical warfare are extensive, and in light of recent use of such agents for targeted attacks, it is important for clinicians to recognize and manage these cases.*

### What is new in the current study

*Potential chemical and biological agents that could be weaponized and the optimal strategies for the diagnosis and treatment of patients exposed to an aerosolized unknown biological or chemical weapon are presented.*

## INTRODUCTION

In the current international political climate, the risk of chemical or biological agent weaponization is undeniably heightened [1–3]. The 1972 Biological Weapons Convention and the 1993 Chemical Weapons Convention established safeguards to limit the use of biological and chemical weapons [4,5]. However, terrorist groups, rogue governmental agencies, or malicious individuals with access to these substances may elect to use the agents at any time. The COVID-19 pandemic has exposed the vulnerability of the American healthcare system to a biological agent [6]. Easily accessible information around advancements in microbiology, genetic engineering technology, and gene editing tools exacerbate the risk of a potential attack [7].

The use of biological agents for bioterrorism warfare extends from the ancient times to the present day; historical accounts document attackers throwing plague corpses over the city walls of Caffa (now Feodosia, Ukraine) during a siege [8]. Other accounts describe poisoning enemy wells with human remains in wartime [9]. Notable examples from the last century include the use of plague, cholera, and typhoid by the Japanese against China during World War II and the use of biological toxins by Iraq against ethnic Kurds and Iran in the 1990s [10,11]. Beyond open warfare, terrorists have used these agents to launch domestic attacks. The most prominent was the 2001 anthrax attacks in which an unknown perpetrator sent *Bacillus anthracis* spores to government officials and private citizens through the US Postal Service [12].

While biological agents are derived from naturally occurring organisms, their chemical counterparts are synthetically produced. The Tokyo subway sarin attack and the use of VX agent in the assassination of Kim Jong-nam have demonstrated the devastation potential of chemical weapons [13,14]. These agents are more common due to their availability and physiologic properties [15]. Unlike biological agents, victims of chemical weapons such as organophosphate nerve agents typically experience rapid onset of classic, easily recognizable symptoms. Despite the high mortality associated with chemical agents, practitioners usually can readily identify their effects. The effects of an exposure to biological agents, however, present later than the effects of chemical agents and often mimic other etiologies of illness. Thus, biological warfare patients present a challenge to clinicians in the recognition of victims, particularly with an aerosolized agent exposure.

In the event of a biological or a chemical bioterrorism agent attack, victims seeking care for symptoms or guidance after a possible exposure will depend on healthcare provider assistance [16]. In this review, we consider the management of a currently asymptomatic patient exposed to an unknown aerosolized substance.

We focus on the evaluation and treatment of a patient with possible aerosolized biological or chemical agent exposure with slow onset. We assume the aerosol is odorless, colorless, and initially unidentified. Based on the available literature and expert opinions, we discuss optimal strategies for the diagnosis and treatment of patients with such an exposure.

## METHODS

PubMed and Scopus databases were searched, and the references of the included studies were also examined to find additional sources. The initial search identified 749 articles, of which 32 were included in this review. Additional references were added at the author's discretion. Inclusion criteria were articles referencing a colorless, odorless, and aerosolized substance with an incubation period of at least 4 hours. Exclusion criteria were substances that cannot be aerosolized; substances with immediate clinical effect; and substances that are easily identifiable upon exposure due to a distinctive color, odor, taste, or texture. Only English language articles were included. We included studies such as systematic reviews, clinical guidelines, and retrospective studies. Data from the included articles were summarized and reported by agent. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors (Supplementary Fig. 1).

## RESULTS

### Nerve agents

#### *Novichok agents*

The relatively newly developed "*Novichok*," meaning "newcomer," or A-series nerve agents are extremely lethal, synthetic chemical weapons. These nerve agents gained notoriety after two recent cases of suspected Novichok poisonings that illustrate the extremely toxic nature of these substances. On August 20th, 2020, Alexei Navalny became seriously ill approximately 1 hour into a flight from Siberia to Moscow. The plane landed emergently in Omsk; however, officials later airlifted Alexei to Germany where tests showed Alexei had been poisoned, presumably with a Novichok agent [17]. Similarly, Sergei and Yulia Skripal were found unconscious on a park bench in Salisbury, England on March 4th, 2018. The time between possible exposure to the nerve agent and their discovery unconscious was suspected to be from 30 minutes to 3 hours [18]. A police officer who responded to the scene also developed symptoms of nerve agent poisoning and was later admitted to the hospital. One month later, the Organization for the Prohibition of Chemical Weapons (OPCW) confirmed Novichok

agent poisoning [19]. In the case of both poisonings, the victims survived because of the quick and efficient actions of those involved [17,18].

These A-series nerve agents are clear, odorless liquids at room temperature and induce a cholinergic crisis by irreversibly inhibiting acetylcholinesterase, the enzyme that degrades acetylcholine. The preceding G-series nerve agents, namely sarin (GB), can cause fatal outcomes in 1 to 10 minutes; VX causes fatalities in 4 to 18 hours [20]. The precise onset of toxicity of A-series agents is not well described; however, given that A-230 is estimated to be five to eight times more toxic than VX and A-232 is estimated to be 10 times more toxic than soman (GD), the onset of symptoms may occur within minutes of inhalation [21]. Like previously developed nerve agents, the Novichok agents cause acetylcholinesterase to undergo an aging process that renders the enzyme permanently inactive if an antidote is not administered in a timely fashion [20]. These agents bind to a serine residue on acetylcholinesterase through phosphorylation. If the nerve agent is not removed via an oxime reaction, an R-alkyl group will eventually become permanently removed and produce molecular aging. The time required for aging to occur depends on the nerve agent and ranges from 2 minutes with the G-series agent soman to greater than 40 hours with VX [22]. Unlike previous nerve agents, Novichok agents also have effects at peripheral nerve synapses which can cause peripheral neuropathy [20].

Exposure to any of the Novichok agents results in a cholinergic toxidrome produced by an excess of acetylcholine at nicotinic, muscarinic, and central nervous system (CNS) receptors [21]. Nicotinic effects can include tachycardia, hypertension, diaphoresis, fasciculations, and muscle weakness. Muscarinic effects can include bradycardia, bronchorrhea, miosis, salivation, lacrimation, nausea and/or vomiting, diarrhea, and increased urination. Last, CNS effects are often the cause of death and can include seizures, respiratory paralysis, and coma [19]. Biological markers to detect acetylcholinesterase and butyrylcholinesterase activity are useful in confirming exposure to these agents [23,24]. Treatment for these agents includes 2 to 6 mg of intravenous atropine (which is a competitive antagonist at muscarinic receptors) every 5 to 10 minutes until bradycardia and/or bronchorrhea resolves, an anticonvulsant such as diazepam, and 1 to 2 grams of intravenous pralidoxime (alternative, 250 mg of obidoxime) every 3 to 6 hours (alternative, continuous infusion lasting at least 24 hours after the last atropine dose is given) [21].

Biological agents

There are several biological agents that have the potential to be aerosolized and used as a weapon. In this review, we will discuss

Table 1. Bioterrorism agents categorized by CDC

Category	Definition
Category A Anthrax Botulism Plague Smallpox Tularemia Viral hemorrhagic fevers <sup>a)</sup>	Organisms that can be easily disseminated or transmitted from person to person; result in high mortality rates and have the potential for major public health impact; might cause public panic and social disruption; and require special action for public health preparedness.
Category B Brucellosis <i>Clostridium perfringens</i> <i>Salmonella</i> , <i>Escherichia coli</i> O157:H7 <i>Shigella</i> Glanders Meliodosis Psittacosis Q fever Ricin toxin Staphylococcal enterotoxin B Typhus fever Viral encephalitis <i>Vibrio cholerae</i> <i>Cryptosporidium parvum</i>	Organisms that are moderately easy to disseminate; result in moderate morbidity rates and low mortality rates; and require specific enhancements of CDC's diagnostic capacity and enhanced disease surveillance.
Category C Nipah virus Hantavirus	Emerging pathogens that could be engineered for mass dissemination in the future because of availability; ease of production and dissemination; and potential for high morbidity and mortality rates and major health impact.

Information from CDC [25].  
CDC, Centers for Disease Control and Prevention.  
<sup>a)</sup>Including filoviruses (Ebola, Marburg) and arenaviruses.

the most likely candidates for use in biological weaponry as categorized by the Centers for Disease Control and Prevention (CDC) (Table 1) [25], and we will review their clinical features and management.

Ricin

Ricin is a well-documented toxin that is derived from the castor bean plant *Ricinus communis*. Ricin has two polypeptide chains, denoted A and B. The toxin enters the cell and exerts its effects by inhibiting protein synthesis. The British Broadcasting Corporation (BBC) journalist Georgi Markov was famously assassinated with a ricin-tipped umbrella in 1978. Saddam Hussein stockpiled the substance; and more recently, Shannon Richardson, an American actress, attempted to send ricin-laced letters to President Barack Obama [26]. Inhalation of this agent is the most dangerous route of exposure, and powdered ricin has the potential to be aerosolized. The powdered form is water soluble, odorless, and tasteless. Onset of symptoms after inhalation of ricin requires approximately 4 to 8 hours. Based on the limited data available, ri-

cin toxicity is expected to present with allergic symptoms such as rhinorrhea and bronchospasm; flu-like symptoms including fever, nausea, cough, shortness of breath, and chest pain; as well as dyspnea and pulmonary edema. There is no readily available diagnostic test for ricin exposure, so treatment should be initiated whenever there is a suspicion of exposure. Treatment involves steroids, antihistamines,  $\beta_2$  adrenergic agonists for allergic symptoms, and supportive care such as continuous positive airway pressure and/or intubation for pulmonary edema [27]. Of note, there is a potential recombinant ricin toxin A subunit (RTA) vaccine, RiVax, currently undergoing US Food and Drug Administration (FDA) trials [28].

### Botulism

Botulism is a disease caused by toxins from *Clostridium botulinum* bacteria. Botulinum toxin is both the most potent toxic agent by weight known and is relatively easy to produce [29,30]. On several occasions in the 1990s, the terrorist group, Aum Shinrikyo, released aerosolized botulinum in multiple failed attacks in Tokyo [31–33]. During the same decade Iraq confessed to having generated a large arsenal of concentrated toxin [31]. Inhalation botulism incubation may be up to 72 hours.

The toxin can be aerosolized into colorless and odorless particles that are 0.1 to 0.3  $\mu\text{m}$  in size [31]. After being absorbed through inhalation, ingestion, or wound penetration into the bloodstream, botulinum toxin acts at the neuromuscular junction of peripheral nerves and prevents acetylcholine release. The disease is characterized by bilateral cranial nerve dysfunction, including diplopia, ptosis, blurred vision, dysphagia, facial weakness, and nystagmus. This is accompanied by symmetrical descending weakness that progresses from the trunk to upper and lower extremities. Respiratory involvement can be caused by upper airway compromise or diaphragmatic paralysis which requires intubation and mechanical ventilation. The diagnosis is established through thorough history-taking and physical exam; antitoxin can be prophylactically administered since confirmatory testing requires 1 to 4 days for identification. Detection of the toxin is mainly made by mouse bioassay in which mice are injected with the specimen. Other techniques to detect the toxin include enzyme-linked immunosorbent assay (ELISA), mass spectroscopy, and polymerase chain reaction (PCR) testing [34,35]. The mainstay treatment of the disease is supportive therapy, respiratory care, and prompt intubation if needed. Another available therapy is heptavalent botulinum antitoxin (HBAT), which, in the United States, is requested through the CDC via local or state departments and the Strategic National Stockpile (SNS) [36]. Evidence shows reduced mortality with early administration of the antitoxin [37,38].

### Anthrax

*Bacillus anthracis*, a gram-positive spore-forming bacteria, causes anthrax. The ability to form spores enables survival for many decades, making the spores highly resistant. In 2001, an unknown offender mailed envelopes containing anthrax spores to multiple offices causing 17 infections and four deaths in the United States [39].

Infection through spore inhalation, ingestion, or inoculation of the mucous membrane or skin results in three major anthrax syndromes: inhalation, cutaneous, and gastrointestinal anthrax [40,41]. Inhaled anthrax has the highest mortality rate of the three and is the most likely type to be used as an aerosolized biological bioterrorism agent [42]. Although usually fatal, inhalational anthrax is rare and most commonly occurs when spores are aerosolized during the processing of contaminated animal products [40]. However, inhalational anthrax is most relevant in this context because intentional aerosolization may be an act of bioterrorism [43]. The incubation period of inhaled anthrax is estimated to be 1 to 7 days [39,44]. The clinical course of infection is biphasic, with a prodromal phase lasting 4 to 5 days, beginning with nonspecific symptoms such as fever, malaise, myalgia, and progressing to more suggestive symptoms including dyspnea, hemoptysis, chest pain, and odynophagia [45]. The second phase is a rapid fulminant bacteremic phase which is manifested by the development of hypoxemia, severe respiratory distress, and shock. This may lead to death within days. Even with intensive care advancement, outcomes during the fulminant phase have not changed; however, initiating antibiotic therapy in the prodromal phase has been shown to improve outcomes [43]. Establishing a diagnosis of anthrax early is crucial because treatment initiation in a narrow, early disease window is necessary. Signs associated with inhalation anthrax include nausea, vomiting, altered mental status, cyanosis, pallor, and hematocrit  $> 45\%$ . Moreover, a chest x-ray demonstrating a widened mediastinum should raise clinical suspicion [46]. The CDC developed recommendations for testing patients with suspected inhalation anthrax, which include collection of blood specimens prior to antimicrobial therapy for culture and PCR testing. Also, since half of patients affected by inhalation anthrax will likely develop meningitis, lumbar puncture is performed for cerebrospinal fluid analysis. When suspicion is high, empiric treatment should include antimicrobial agents such as ciprofloxacin plus clindamycin or linezolid. If anthrax with CNS involvement is suspected, triple therapy with ciprofloxacin plus meropenem and linezolid is recommended. Penicillin G is equivalent to fluoroquinolone in anthrax strains that are susceptible. Antitoxin or anthrax immunoglobulin is an essential part of the therapeutic regimen [43]. For postexposure prophylaxis, exposed individuals are indicated to receive

an anthrax vaccine and an antimicrobial drug course which includes either doxycycline or ciprofloxacin.

### Tularemia

Tularemia, alternatively referred to as Rabbit Fever, is caused by the gram-negative zoonotic bacteria *Francisella tularensis*. This disease has a documented history of use in biological weapon programs and was previously stockpiled in US facilities from 1954 to 1955. These stockpiles were destroyed in 1973. Tularemia is considered as a dangerous weaponizable biologic agent due to its ability to be aerosolized and cause considerable morbidity and mortality. The clinical presentation of tularemia varies depending on the site and route of exposure, but notably causes symptoms of pneumonia after 3 to 5 days following an aerosol exposure [48]. This form of tularemia is more severe, with mortality rates of 30%. Presenting symptoms include hilar adenopathy, dry cough, shortness of breath, and chest pain. Tularemic sepsis may occur with severe infection, is often fatal, and may cause shock or disseminated intravascular congestion. Infection is confirmed via serology,

and treatment includes streptomycin or gentamicin for a duration of 10 days. Alternative treatments include doxycycline, chloramphenicol, and ciprofloxacin [48].

### Psittacosis

Widely known as Parrot Fever, psittacosis is caused by *Chlamydo-phila psittaci*. This disease is often described in relation to bird ownership or exposure but does have the potential to be aerosolized to cause infection. The CDC has classified *C. psittaci* as a class B biological warfare agent for this reason. While there have been no documented uses of this agent to intentionally cause disease, the United States, the former Soviet Union, and Egypt have all researched its potential as a biological weapon. Psittacosis causes atypical pneumonia and has a nonspecific clinical presentation. The incubation period ranges from 1 to 3 days with direct local invasion of the pulmonary parenchyma, and more commonly, 7 to 15 days when a primary bacteremia occurs that leads to infection within the reticuloendothelial system. Due to the range in symptom onset, disaster medicine experts predict that a *C. psittaci*

**Table 2.** Summary of agent mechanism of action, clinical presentation, and treatment

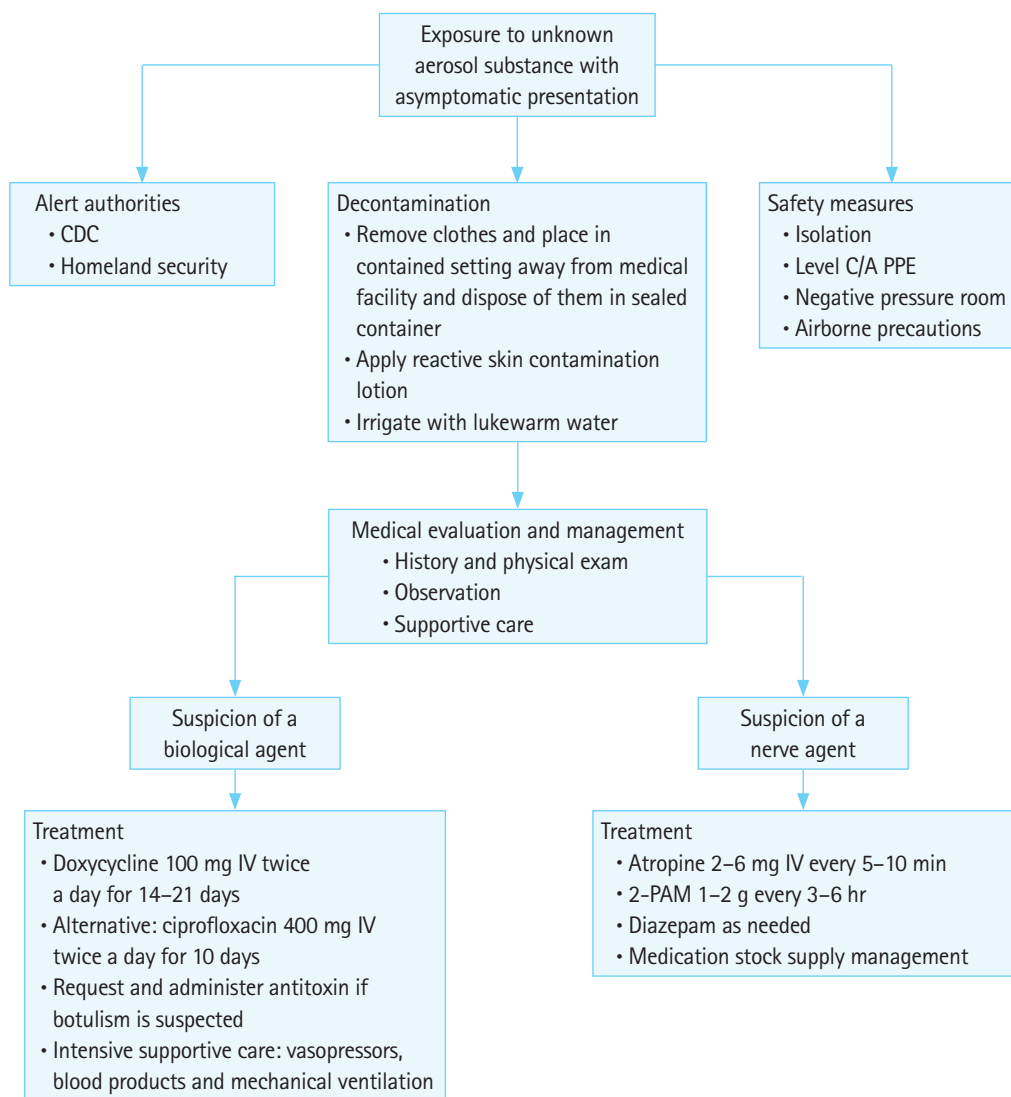
Agent name	Mechanism of action	Clinical presentation	Treatment
Novichok	Inhibition of acetylcholinesterase leading to accumulation of acetylcholine in the synapse.	Cholinergic syndrome (SLUDGEM)	IV atropine every 5–10 min until bradycardia and/or bronchorrhea resolves. IV pralidoxime every 3–6 hr. Diazepam for seizure prevention as needed.
Ricin	Inhibition of protein synthesis by ribosome-inactivating protein leading to cell death.	Rhinorrhea, bronchospasm, fever, nausea, cough, shortness of breath, chest pain, and pulmonary edema.	For allergic symptoms treatment involves steroids, antihistamines, and $\beta_2$ adrenergic agonists. For pulmonary edema, treatment with CPAP or mechanical ventilation.
Botulism	Presynaptic inhibition of acetylcholine release in the neuromuscular junction causing paralysis.	Cranial nerve dysfunction: diplopia, ptosis, blurred vision, dysphagia, facial weakness, and nystagmus. Accompanied by symmetrical descending weakness that progresses from the trunk to upper and lower extremities. Respiratory involvement can cause diaphragmatic paralysis.	HBAT. Intubation if needed. Supportive care.
Anthrax	Toxicity from anthrax is mediated through two toxins. Edema toxin, which is a calcium-bound calmodulin-stabilized toxin leading to accumulation of cAMP and activating many cellular pathways. Lethal toxin, a zinc metallo-protease leading to cell death by inhibition of MAP kinase pathway.	Fever, malaise, myalgia, dyspnea, hemoptysis, chest pain, and odynophagia. Progress to hypoxemia, severe respiratory distress, and shock.	Antimicrobial treatment with a combination of ciprofloxacin+clindamycin or linezolid. If CNS is involved, then treatment with combination of ciprofloxacin + meropenem + linezolid.
Tularemia	Pathogenesis is mediated through acute inflammatory response. For its survival, several virulent factors aid with preventing phagosome-lysosome fusion and complement-mediated lysis.	Dry cough, shortness of breath, and chest pain. Progress to septic shock and DIC.	Antimicrobial treatment with streptomycin or gentamicin. Alternative treatment: doxycycline, chloramphenicol, and ciprofloxacin.
Psittacosis	Enters mucosal epithelial cells in its elementary body form. Relying on host cell, the organism replicates inside in its reticulate body form, which causes cell death.	Dry cough, fever, malaise, vomiting, diarrhea, headache, and anorexia.	Antimicrobial treatment with doxycycline.

SLUDGEM, salivation, lacrimation, urination, defecation, gastric hypermotility, emesis, and miosis; IV, intravenous; CPAP, continuous positive airway pressure; HBAT, heptavalent botulinum antitoxin; cAMP, cyclic adenosine monophosphate; MAP, mitogen activated protein; CNS, central nervous system; DIC, disseminated intravascular coagulation.

ci epidemic would result in a bimodal spike of cases, with a slightly greater second peak. Fortunately, this disease does have a lower mortality rate of roughly 20% without treatment and 1% with timely intervention. Generalized symptoms include a cough (most often a dry cough with little to no sputum), fever and malaise, vomiting and diarrhea, headache, and anorexia. Physical examination findings may include fever, rales, tachypnea, and consolidation that can be seen via chest X-ray. Serologic testing is the preferred method for diagnosis, but PCR may also be used. Oral doxycycline and tetracycline are the preferred treatments. For severely ill patients, intravenous doxycycline may be used. Azithromycin has also been shown in animal models to potentially be an effective alternative treatment (Table 2) [49].

## DISCUSSION

The availability, relatively low cost, and potential for devastating impact make chemical and biological agents increasingly appealing for those striving to inflict terror and destruction. Despite multiple attempts within the international community to limit and prevent their use, these weapons continue to appear and are more likely to be used during times of political upheaval. Given the current sociopolitical climate both nationally and abroad, clinicians need to maintain readiness for a potential attack. Particularly in the event of exposure to an unknown aerosolized substance, clinicians should be aware of the possible types of biological and chemical agent exposures and a safe approach to the asymptomatic patient. In addition, incubation periods may complicate the



**Fig. 1.** Approach to asymptomatic patient presentation in the emergency department with exposure to unknown aerosol substance. CDC, Centers for Disease Control and Prevention; PPE, personal protective equipment; IV, intravenous; 2-PAM, pralidoxime.

clinical picture as patients may not present for several days post-exposure. This also underscores the importance of real-time surveillance and reporting for suspicious cases.

Before completing a thorough patient evaluation, two essential elements of patient and facility management are decontamination and containment [50]. With any aerosolized substance exposure, patients and providers must maintain airborne precautions until additional details are determined. For suspected chemical agents, providers should initiate a mass casualty decontamination protocol [51]. This may occur differently depending on the hospital facility and the agent suspected. The UK Initial Operational Response (IOR) recommends the rinse-wipe-rinse method to quickly decontaminate individuals after an exposure. An approach to the asymptomatic patient presenting to the emergency department after exposure to an unknown aerosol is shown in Fig. 1. Patients must remove all clothing to be placed in a sealed plastic bag. While many hospitals have at least small-scale showers available for decontamination, others may have larger facilities such as tents. Dry contamination using various products such as fullers earth or "blue roll" is also possible. Of note, providers should avoid dry bleach powder in cases of suspected Novichok agent exposures as it may release toxic metabolites [19].

As in any other medical evaluation, history and physical examination are fundamental, with attention to clustering of cases. Incubation periods for biological agents range from 24 hours to 16 days. Patients may not be symptomatic at the time of their evaluation or may present later without ready recall of their exposure. Diagnostic testing is minimally impactful in the assessment of nerve agent exposure. No further testing currently offers clinically relevant data pertaining to these agents specifically although new developments in mass spectrometry may change diagnostic capabilities in the future [52,53]. Potential biological markers such as phosphorylated butyrylcholinesterase are useful in detecting nerve agent exposure [24,54].

Specific microbe testing for biological agents with respiratory toxidromes is minimally available and prohibitively costly. There is a need for the development of accurate and efficient diagnostic panels or tests [55,56]. If collateral information to suggest a specific microbe exists, such as other known cases in the community, most require a specific ELISA or PCR. While some have specific toxidromes such as the neurological symptoms seen with *C. botulinum* or the hemorrhagic fever associated with Ebola or Marburg viruses, many of these patients initially present with symptoms of respiratory infection. Important consideration of the progression of symptoms is required as higher mortality diagnoses tend to progress more quickly.

Many factors can affect the management approach to individ-

uals with aerosol exposure, which include the victim's characteristics, presence of comorbidity, immune status, patterns of other known incidents, and description of the event. Moreover, the approach can differ in certain patients who are considered to have high-risk targetability such as public figures. When identified, these biological agents can be treated with antibiotics and supportive care. Most are susceptible to doxycycline and ciprofloxacin. Other agents, such as botulinum toxin, can be treated with supportive care and antitoxin whenever symptoms arise.

In the case of asymptomatic aerosol exposure, similar decontamination and containment methods should be considered alongside a high suspicion for a chemical or a biological attack [50]. Administration of atropine, pralidoxime and an anticonvulsant (diazepam) can be initiated if a cholinergic toxidrome develops during patient evaluation. In cases of massive exposure, which require large doses of atropine and pralidoxime to reverse acetylcholinesterase inhibition, a logistical plan to identify an alternative medication supply should be considered, such as deployment of the resources from the CDC SNS [57].

In the future, perpetrators may weaponize other biological agents that cannot currently be aerosolized, such as arenavirus, bunyavirus, flavivirus, marine toxin, and *Orientia tsutsugamushi* (scrub typhus). Similar to the development of Novichok, employing any of these agents can have catastrophic effects. Biological agents, while rarely utilized in a real-world attack, could have devastating consequences.

## SUPPLEMENTARY MATERIALS

**Supplementary Fig. 1.** Flowchart of search results, study inclusion, and exclusion.

Supplementary material is available from <https://doi.org/10.15441/ceem.22.412>.

## ETHICS STATEMENTS

Not applicable.

## CONFLICT OF INTEREST

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

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Conceptualization: AP, RA; Data curation: AP, RA, HC; Formal analysis: all authors; Methodology: AP, RA, NS; Project administration: AP, RA; Writing—original draft: all authors; Writing—review & editing: all authors. All authors read and approved the final manuscript.

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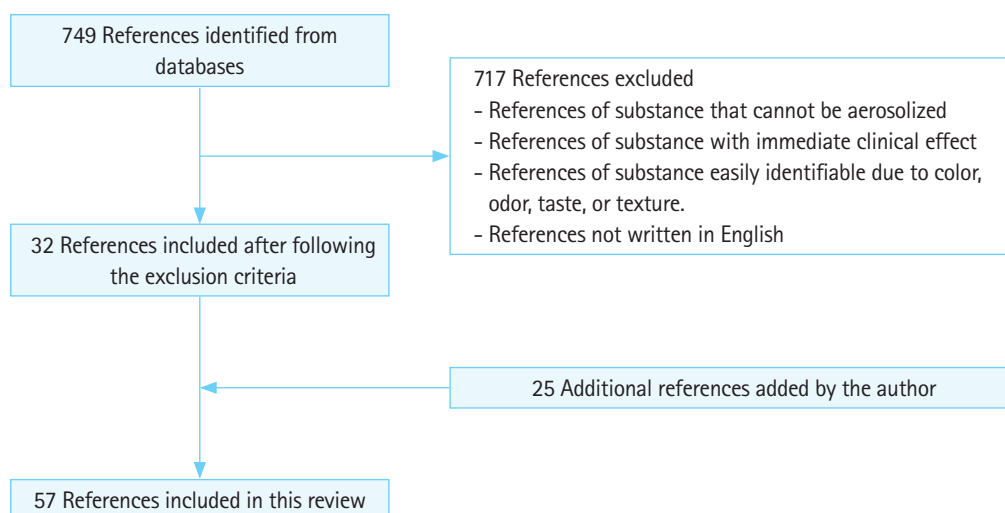
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**Supplementary Fig. 1.** Flowchart of search results, study inclusion, and exclusion.

# Mortality among adult patients with sepsis and septic shock in Korea: a systematic review and meta-analysis

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**Objective** To evaluate mortality from sepsis and septic shock in Korea during the past 10 years, we conducted a systematic review and meta-analysis.

**Methods** We searched six databases for studies on mortality from sepsis and septic shock in adult patients. Primary outcomes were 28- or 30-day mortality and in-hospital mortality from sepsis and septic shock. To assess the risk of bias, we used the Newcastle-Ottawa Scale and Risk of Bias 2 tools. The protocol is registered in PROSPERO (No. CRD42022365739).

**Results** A total of 61 studies were included. The mortality rates from sepsis and septic shock at 28 or 30 days were 22.7% (95% confidence interval [CI], 20.0%-25.6%;  $I^2 = 89\%$ ) and 27.6% (95% CI, 22.3%-33.5%;  $I^2 = 98\%$ ), respectively, according to the Sepsis-3 criteria. Furthermore, in accordance with the Sepsis-3 criteria, the in-hospital mortality rates were 28.1% (95% CI, 25.2%-31.1%;  $I^2 = 87\%$ ) and 34.3% (95% CI, 27.2%-42.2%;  $I^2 = 97\%$ ), respectively.

**Conclusion** The mortality rates from sepsis and septic shock in Korea are high. In the case of septic shock, the in-hospital mortality rate is approximately 30%.

**Keywords** Sepsis; Septic shock; Mortality; Republic of Korea; Meta-analysis

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## Capsule Summary

### What is already known

Mortality rates for sepsis and septic shock vary between studies. To appropriately determine the mortality rate from sepsis and septic shock in Korea, it is necessary to conduct a systematic review and meta-analysis.

### What is new in the current study

This is the first meta-analysis of published sepsis and septic shock mortality rates in Korea. Sepsis mortality in Korea was similar or higher than in the United States and Europe, whereas septic shock mortality was lower.

## INTRODUCTION

Sepsis is a life-threatening multiorgan dysfunction caused by an inappropriate host response to infection [1]. Despite global efforts to minimize its lethality, sepsis remains the leading cause of death in critically ill patients and a burden on patients and healthcare systems worldwide [1–3]. Through campaigns to reduce the mortality rate of sepsis, experts in various fields have improved the survival rate by defining the Sepsis-3 diagnostic criteria and promoting adherence to recommended treatment protocols [1,4,5]. A total of 48.9 million incident cases and 11.0 million sepsis-related deaths have been reported in 2017, accounting for approximately 20% of global deaths during that time [2]. A recent meta-analysis showed that the pooled mortality rate of sepsis is 19.6% in North America, 23.6% in Europe, 18.7% in Australia, and 29.0% in China [6,7]. The mortality rates differ across countries because of disease severity, study type, period, and region, but different standard care protocols and health care systems also significantly affect the care and prognosis of patients with sepsis [6].

In Korea, previous research analyzing national health insurance data revealed sepsis mortality rates ranging from 17.5% to 30% [8–10]. However, those studies evaluated sepsis or septic shock based on diagnostic International Classification of Diseases, 10th Revision (ICD-10) codes in insurance records, not the sepsis criteria. Thus, their study populations might differ from the population described by the sepsis criteria and inaccurately depict sepsis mortality. Despite the large number of multicenter and single-center studies on sepsis and septic shock, including some multicenter registries, no previous studies in Korea reflect the overall sepsis fatality rate, to the best of our knowledge. To appropriately determine the mortality rate from sepsis and septic shock in Korea, a systematic review and meta-analysis are required. Therefore, we investigated the sepsis and septic shock mortality rates published for Korea during the past 10 years and analyzed those rates based on the Sepsis-3 criteria.

## METHODS

### Reporting guidelines and protocol registration

This study adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) and the MOOSE (Meta-Analysis of Observational Studies in Epidemiology) guidelines for reporting information from observational studies [11,12]. This review protocol is prospectively registered in PROSPERO (No. CRD42022365739).

### Search strategy

We systematically searched the PubMed, Embase, Cochrane Library, KMBASE (Korean Medical Database), KoreaMed, and KISS (Korean Studies Information Service System) databases for studies about mortality and the frequency of sepsis and septic shock in adult patients that were published between January 2012 and July 2022. As our search strategy, we combined medical subject headings terms and free terms related to "sepsis," "septic shock," and "South Korea" and included Embase subject headings and text words. The detailed search strategy is presented in Supplementary Table 1.

### Study selection

We selected studies through title and abstract screening and used the following inclusion criteria: confirmed sepsis, severe sepsis or septic shock in adult patients according to the Sepsis-1, -2, or -3 criteria, and studies conducted in Korea and published between January 1, 2012 and September 23, 2022. We excluded studies with insufficient data and those involving sepsis patients from specific disease groups, reviews, case reports, editorials, letters, conference abstracts, meta-analyses, and animal studies. To prevent duplicate data, we selected studies with the longest study period and largest sample size when we found multiple studies that shared the same registry or institution.

### Data extraction

Two reviewers independently extracted the relevant data about the patients in the included studies, and discrepancies between reviewers were discussed and resolved by consensus. We extracted the following variables: publication data; study design and settings; patient information—number of participating centers, patient locations (emergency room, ward, or intensive care unit [ICU]), number of patients, and deaths; sepsis diagnostic criteria; and the time of outcome measurement (28- or 30-day mortality and in-hospital mortality).

### Quality assessment of individual studies

The Newcastle-Ottawa Scale, which divides an eight-item score into three domains, was used to evaluate nonrandomized studies [13]. The Risk of Bias 2 tool was used to evaluate randomized controlled trials [14]. Each article was rated based on selection (maximum, four stars), comparability (maximum, two stars), and outcome (maximum, three stars). Both reviewers assessed the 61 included studies independently. Unresolved disagreements between reviewers were resolved by discussion or consultation with a third reviewer.

Table 1. Characteristics of the studies included in the systematic review and meta-analysis

Study	Study design	Study period	No. of centers	Patient location	Cohort screened	Outcome	Diagnostic criteria	Study details
Cha et al. [15] (2022)	Retrospective cohort study	Nov 2013–May 2017	1	ICU	Patients ≥ 18 yr, ICU LOS > 3 day with sepsis and septic shock	30-Day, in-hospital	Sepsis-3	Investigation of the effects of nutritional support on clinical prognosis
Cho et al. [16] (2012)	Prospective cohort study	Sep 2007–Nov 2010	1	General ward, ICU	Patients suspected of sepsis in either the general wards or ICU	28-Day, in-hospital	Other	Assessment of the prognostic power of lysophosphatidylcholine for sepsis
Choi et al. [17] (2020)	Retrospective cohort study	Mar 2015–Jun 2018	1	ICU	Patients > 18 yr, admitted to the medical ICU with sepsis	28-Day, in-hospital	Sepsis-3	Clinical value of full-length tryptophanyl-tRNA synthetase for sepsis detection
Choi et al. [18] (2021)	Retrospective cohort study	Mar 2008–Dec 2017	1	General ward, ICU	General rapid response system treatment in hospital wards	28-Day, in-hospital	Sepsis-3	Investigation of the effects of the rapid response system on outcomes in patients with septic shock
Chung et al. [19] (2019)	Prospective cohort study	Mar 2010–Jun 2016	1	ED	Patients ≥ 18 yr, with severe sepsis or septic shock	28-Day	Other	Evaluation of the association between monocyte counts and mortality
Hong et al. [20] (2016)	Retrospective cohort study	Nov 2012–Sep 2014	1	ED	Patients ≥ 18 yr, with sepsis and without dialysis	28-Day	Other	Assessment of neutrophil gelatinase-associated lipocalin as a prognostic biomarker for hospital mortality in patients with sepsis in EDs
Hong et al. [21] (2020)	Retrospective cohort study	Sep 2015–Feb 2019	1	ICU	Patients ≥ 18 yr, with sepsis or septic shock who underwent echocardiography	28-Day	Sepsis-3	Effects of left ventricular dysfunction and fluid balance on the outcomes of patients with sepsis
Huh et al. [22] (2013)	RCT	Aug 2007–Jan 2009	1	ED	Patients ≥ 18 yr, with severe sepsis or septic shock	In-hospital	Other	Comparison of clinical outcomes between intermittent and continuous monitoring of central venous oxygen saturation
Hwang et al. [23] (2018)	Retrospective cohort study	Aug 2008–Sep 2014	1	ED	Patients ≥ 18 yr, diagnosed with severe sepsis or septic shock	28-Day, in-hospital	Other	Evaluation of the diagnostic value of the qSOFA score for mortality in septic patients
Hwang et al. [24] (2019)	Retrospective cohort study	Aug 2008–Sep 2016	1	ED	Patients ≥ 18 yr, with septic shock	28-Day	Other	Investigation of the effect of antibiotic timing on the outcomes of sepsis
Hwang et al. [25] (2020)	RCT	Dec 2018–Jan 2020	6	ED	Patients (19–89 yr) with septic shock	28-Day, in-hospital	Sepsis-3	Evaluation of the effects of early combination therapy with intravenous vitamin C and thiamine in patients with septic shock
Im et al. [26] (2020)	Prospective cohort study	Apr 2014–Jan 2019	1	ICU	Patients ≥ 19 yr, admitted to the medical ICU with sepsis or septic shock	28-Day, in-hospital	Sepsis-3	Association of plasma exosomes with severity of organ failure and mortality in patients with sepsis
Im et al. [27] (2021)	Prospective cohort study	Apr 2014–Jan 2019	1	ICU	Patients ≥ 19 yr, with sepsis admitted to the medical ICU	28-Day, in-hospital	Sepsis-3	Evaluation of the association between exosomal CD63 level and clinical outcomes in patients with sepsis
Im et al. [28] (2022)	Prospective cohort study	Sep 2019–Dec 2020	19 <sup>a)</sup>	ED	Patients ≥ 19 yr, diagnosed with sepsis or septic shock	In-hospital	Sepsis-3	Evaluation of the effects of time-to-antibiotics on in-hospital mortality in patients with sepsis
Jang et al. [29] (2016)	Retrospective cohort study	Jan 2013–Jun 2015	1	ED	Patients ≥ 19 yr, suspected to have sepsis and admitted to the ICU	28-Day	Other	Comparison of the usefulness of the PIRO score and MEDS score in predicting the mortality of septic patients
Jang et al. [30] (2020)	Retrospective cohort study	Mar 2010–Apr 2017	1	ED	Patients ≥ 18 yr, with sepsis or septic shock	28-Day	Other	Investigation of the association between initial phosphate concentration and mortality in patients with sepsis
Jang et al. [31] (2021)	Retrospective cohort study	May 2014–Apr 2018	3	ED	Patients ≥ 18 yr, with sepsis or septic shock	28-Day	Other	Investigation of the relationship between the serum total cholesterol concentration and the outcomes of sepsis patients
Jee et al. [32] (2020)	Retrospective cohort study	Nov 2016–Dec 2016	1	ED	Patients ≥ 18 yr, diagnosed with sepsis	In-hospital	Sepsis-3	Comparison of the mortality rates of patients with early-identified sepsis and late-identified sepsis
Jeon et al. [33] (2019)	Retrospective cohort study	Jan 2018	19 <sup>a)</sup>	ED	Patients ≥ 19 yr, with sepsis	In-hospital	Sepsis-3	Investigation of the characteristics, management, and clinical outcomes of sepsis patients
Jeong et al. [34] (2019)	Prospective cohort study	Jan 2011–Jun 2017	1	ICU	Patients ≥ 18 yr, with sepsis who stayed in the ICU for more than 7 day	28-Day	Other	Relationship between nutrition intake and mortality in patients with sepsis

(Continued on the next page)

Table 1. (Continued)

Study	Study design	Study period	No. of centers	Patient location	Cohort screened	Outcome	Diagnostic criteria	Study details
Jeong et al. [35] (2020)	Retrospective cohort study	Jun 2018–Apr 2019	1	ED	Patients ≥ 19 yr, with sepsis	30-Day	Sepsis-3	Investigation of the efficacy of the albumin-adjusted ischemia-modified albumin level to predict mortality in patients with sepsis
Jung et al. [36] (2019)	Prospective cohort study	Jun 2012–Dec 2016	1	ED	Patients ≥ 18 yr, with septic shock	28-Day	Other	Evaluation of relationship between low hemoglobin levels and mortality in patients with septic shock
Kim et al. [37] (2012)	Prospective cohort study	Jul 2009	25	ICU	Patients admitted to an ICU for severe sepsis	28-Day, in-hospital	Other	Investigation of the influence of full-time intensivist and nurse to patient ratio on the implementation of severe sepsis bundles
Kim et al. [38] (2013)	Prospective cohort study	Jul 2010–Jan 2011	22	ICU	Patients ≥ 18 yr, with severe sepsis or septic shock	28-Day	Other	Comparison of clinical outcomes between pneumonia and other infections in patients with sepsis
Kim et al. [39] (2017)	Retrospective cohort study	Dec 2014–Jun 2015	1	ED, ICU	Patients diagnosed with sepsis	30-Day, in-hospital	Sepsis-3	Investigation of the prognostic utilities of multiple biomarkers for mortality in septic patients
Kim et al. [40] (2019)	Retrospective cohort study	Sep 2018–Aug 2019	1	ICU	Patients ≥ 19 yr, with septic shock who were treated with the vitamin C protocol	28-Day, in-hospital	Sepsis-3	To identify septic phenotypes in patients receiving vitamin C, hydrocortisone, and thiamine using temperature and white blood cell count
Kim et al. [41] (2019)	Retrospective cohort study	Jun 2011–Aug 2017	1	ICU	Patients ≥ 18 yr, diagnosed with sepsis who underwent abdominal CT	In-hospital	Sepsis-3	Investigation of association between skeletal muscle mass and clinical outcomes in patients with sepsis
Kim et al. [42] (2020)	Retrospective cohort study	Aug 2016–Aug 2017	1	Not mentioned	Patients diagnosed with sepsis or septic shock	30-Day	Sepsis-3	Investigation of prognostic value of proenkephalin for renal failure and mortality in patients with sepsis
Kim et al. [43] (2020)	Retrospective cohort study	Jan 2016–Sep 2019	1	ED	Patients ≥ 18 yr, with septic shock	In-hospital	Other	Evaluation of the prognostic value of the inferior vena cava diameter ratio measured on CT in patients with septic shock.
Kim et al. [44] (2020)	Prospective cohort study	Sep 2009–Jun 2015	1	ICU	Patients ≥ 18 yr, ICU LOS > 1 day with sepsis	30-Day, in-hospital	Other	To identify the risk factors of sepsis-associated delirium and its effects on patient outcomes in ICU patients
Kim et al. [45] (2020)	Retrospective cohort study	Jan 2015–Jun 2018	1	ICU	Patients ≥ 18 yr, with septic shock who underwent echocardiography	In-hospital	Sepsis-3	Association between left ventricular systolic dysfunction and mortality in patients with septic shock
Kim et al. [46] (2021)	Retrospective cohort study	Jan 2016–Feb 2019	1	ED	Patients ≥ 18 yr, with sepsis	28-Day	Sepsis-3	Investigation of the prognostic value of a modified simple scoring system based on the red cell distribution width, delta neutrophil index, and mean platelet volume to platelet count ratio in predicting the mortality of patients with sepsis
Kim et al. [47] (2022)	Prospective cohort study	Mar 2019–Jun 2020	1	ICU	ICU patients with sepsis	In-hospital	Sepsis-3	Assessment of the prognostic power of estimated plasma volume status in critically ill patients with sepsis
Kim et al. [48] (2022)	Retrospective cohort study	Oct 2015–Dec 2019	12 <sup>(a)</sup>	ED	Patients ≥ 19 yr, with septic shock	28-Day	Sepsis-3	Evaluation of prognostic factors for late death in septic shock survivors
Kim et al. [49] (2022)	Prospective cohort study	May 2016–May 2020	1	ED	Patients ≥ 18 yr, with suspected or confirmed septic shock	28-Day	Sepsis-3	Investigation of the effects of myosteatosis percentage on mortality in patients with septic shock
Ko et al. [50] (2018)	Prospective cohort study	Oct 2015–Feb 2017	10 <sup>(b)</sup>	ED	Patients ≥ 19 yr, with septic shock	28-Day, in-hospital	Sepsis-3	Evaluation of the prognosis of septic shock patients based on their lactate levels after initial fluid resuscitation
Ko et al. [51] (2019)	Prospective cohort study	Jun 2015–Dec 2016	1	ED	Patients ≥ 18 yr, with septic shock	30-Day	Other	Investigation of the association between the thrombotic microangiopathy score and 30-day mortality among patients with early-stage septic shock
Ko et al. [52] (2020)	Prospective cohort study	Oct 2015–Dec 2017	10 <sup>(b)</sup>	ED	Patients ≥ 19 yr, with suspected or confirmed infection and evidence of refractory hypotension or hypoperfusion	In-hospital	Sepsis-3	Evaluation of the association between antibiotic administration timing and in-hospital mortality in septic shock patients

(Continued on the next page)

Table 1. (Continued)

Study	Study design	Study period	No. of centers	Patient location	Cohort screened	Outcome	Diagnostic criteria	Study details
Lee et al. [53] (2012)	Retrospective cohort study	Jan 2010–Dec 2010	1	ED	Patients ≥ 18 yr, with severe sepsis	28-Day	Other	Investigation of the association between nutritional risk and mortality in severe sepsis patients
Lee et al. [54] (2013)	Prospective cohort study	Jul 2008–Jun 2011	1	ED	Patients ≥ 18 yr, with severe sepsis or septic shock	28-Day	Other	Investigation of the association between hypoalbuminemia and mortality in patients with severe sepsis and septic shock
Lee et al. [55] (2017)	Retrospective cohort study	Oct 2015–Apr 2016	1	ED	Patients ≥ 19 yr, with sepsis	30-Day	Sepsis-3	Investigation of the efficacy of red cell distribution width as a prognostic factor for Sepsis-3 patients
Lee et al. [56] (2018)	Retrospective cohort study	Mar 2007–Feb 2016	1	ED	Patients ≥ 18 yr, sepsis who underwent abdominal CT	28-Day	Sepsis-3	Evaluation of the association between muscle mass depletion and outcomes in sepsis patients
Lee et al. [57] (2021)	Prospective cohort study	Mar 2010 – Nov 2017	1	ED	Patients ≥ 18 yr, diagnosed with sepsis or septic shock	28-Day	Sepsis-3	Investigation of the association among the respiratory rate, oxygenation index, and mortality in patients with sepsis or septic shock
Lee et al. [58] (2021)	Retrospective cohort study	Jan 2016–Dec 2019	1	ED	Patients ≥ 19 yr, with sepsis and septic shock	30-Day	Sepsis-3	Investigation of the prognostic value of lactate levels and lactate clearance in sepsis and septic shock with initial hyperlactatemia
Lee et al. [59] (2022)	Prospective cohort study	Sep 2019–Feb 2020	16 <sup>a)</sup>	ED	Patients ≥ 19 yr, with sepsis	28-Day, in-hospital	Sepsis-3	Investigation of the association between preexisting clinical frailty and clinical outcomes in patients with sepsis
Oh et al. [60] (2017)	Retrospective cohort study	Jan 2010–Dec 2015	1	ED	Patients ≥ 18 yr, with severe sepsis or septic shock	28-Day	Sepsis-3	Assessment of the association between the serum chloride level and mortality in patients with severe sepsis or septic shock
Oh et al. [61] (2019)	Retrospective cohort study	Nov 2007–Mar 2016	1	ED	Patients ≥ 18 yr, with septic shock treated with early goal-directed therapy	28-Day	Other	Assessment of the prognostic significance of the lactate level in septic shock patients
Park et al. [62] (2012)	Prospective cohort study	Apr 2005–Feb 2009	12	ED, ICU	Patients ≥ 18 yr, with severe sepsis or septic shock	28-Day, in-hospital	Other	Investigation of clinical outcomes of ICU patients with community-acquired severe sepsis and septic shock
Park et al. [63] (2012)	Retrospective cohort study	Jan 2008–Dec 2010	1	ICU	Patients admitted to the medical ICU for sepsis	30-Day, in-hospital	Other	Investigation of the association between mild hypoglycemia and hospital mortality
Park et al. [64] (2015)	Prospective cohort study	Jan 2005–Jun 2007, Dec 2007–Jun 2008	1	ED	ED patients with severe sepsis and septic shock	In-hospital	Other	Validation assessment of the low oxygen extraction ratio to predict mortality
Park et al. [65] (2020)	Retrospective cohort study	Jan 2017–Jul 2018	1	ED	Patients ≥ 18 yr, with septic shock	28-Day	Other	Evaluation of the effects of early combination therapy with vitamin C and thiamine on ICU delirium-free days in patients with septic shock
Ryoo et al. [66] (2015)	Prospective cohort study	Jan 2010–Dec 2012	1	ED	Adult patients with sepsis who received early goal-directed therapy	28-Day	Other	Validation assessment of the MISSED score to predict mortality in patients with severe sepsis and septic shock
Ryoo et al. [67] (2019)	Prospective cohort study	Oct 2015–Dec 2017	10 <sup>b)</sup>	ED	Patients ≥ 18 yr, with septic shock	28-Day	Sepsis-3	Assessment of the prognostic value of lactate normalization
Song et al. [68] (2012)	Retrospective cohort study	Aug 2008–Jul 2010	1	ED	Sepsis patients ≥ 18 yr, without hypotension or hypoperfusion	In-hospital	Other	Investigation of factors for predicting early deterioration in sepsis patients with intermediate levels of serum lactate
Song et al. [69] (2021)	Retrospective cohort study	Jan 2016–31 Mar 2020	1	ED	Patients ≥ 18 yr, with sepsis	30-Day	Sepsis-3	Investigation of the association between the vasoactive-inotropic score and mortality in patients with sepsis
Suh et al. [70] (2013)	Retrospective cohort study	Jan–Dec 2010	1	ED	Patients ≥ 18 yr, with sepsis or septic shock excluding chronic renal replacement	In-hospital	Other	Investigation of the clinical characteristics of acute kidney injury in patients with sepsis and septic shock

(Continued on the next page)

Table 1. (Continued)

Study	Study design	Study period	No. of centers	Patient location	Cohort screened	Outcome	Diagnostic criteria	Study details
Um et al. [71] (2018)	Prospective cohort study	Mar 2010–Sep 2016	1	ED	Patients ≥ 18 yr; with sepsis or septic shock	28-Day	Other	Evaluation of the relationship between the time to positivity blood culture and mortality in patients with sepsis and septic shock
Wang et al. [72] (2021)	Retrospective cohort study	Mar 2016–Dec 2018	3	ED	Patients ≥ 18 yr; with sepsis	28-Day, in-hospital	Sepsis-3	Association between health insurance status and outcomes of sepsis in adult patients
Yeo et al. [73] (2022)	Prospective cohort study	Sep 2019–Feb 2020	16 <sup>a)</sup>	Not mentioned	Patients with septic shock	28-Day, in-hospital	Sepsis-3	Evaluation of the effect of administering a vasopressor within 1 hr of first fluid loading on clinical outcomes in septic shock patients
Yoo et al. [74] (2020)	Prospective cohort study	Mar–Dec 2018	1	ICU	Patients with sepsis who were admitted to the medical ICU	30-Day	Other	Evaluation of the association between 25(OH) D and vitamin D binding protein levels and sepsis mortality
You et al. [75] (2022)	Prospective cohort study	Nov 2015–Dec 2017	11 <sup>b)</sup>	ED	Patients > 18 yr; with septic shock	28-Day, in-hospital	Sepsis-3	Investigation of the rate of compliance with the surviving sepsis campaign 3-hr bundle for nighttime and daytime ED admissions and the clinical effects of compliance on mortality in patients with septic shock

ICU, Intensive care unit; LOS, length of stay; tRNA, transfer RNA; ED, emergency department; RCT, randomized controlled trial; qSOFA, quick Sequential Organ Failure Assessment; PIRO, predisposition, infection, response, and organ dysfunction; MEDS, Mortality in Emergency Department Sepsis; CT, computed tomography; MISSED, Mortality in Severe Sepsis in the Emergency Department.

<sup>a)</sup>Korean Sepsis Alliance (KSA) registry. <sup>b)</sup>Korean Shock Society (KoSS) registry.

Table 2. Subgroup analyses for sepsis and septic shock

Characteristic	Mortality			
	No. of studies	Proportion (95% CI)	P-value <sup>a)</sup>	I <sup>2</sup> (%)
Sepsis				
28- or 30-day mortality				
Sepsis criteria				
Sepsis-3	17	22.7 (20.0–25.6)	< 0.01	89
Other	10	29.1 (23.3–35.6)	< 0.01	97
Study design				
Retrospective	17	22.6 (19.5–25.9)	< 0.01	94
Prospective	10	29.1 (23.4–35.5)	< 0.01	96
Included hospital				
Single center	22	23.3 (20.5–26.5)	< 0.01	93
Multicenter	5	31.3 (22.1–27.7)	< 0.01	98
In-hospital mortality				
Sepsis criteria				
Sepsis-3	13	28.1 (25.2–31.1)	< 0.01	87
Other	4	21.6 (9.2–30.5)	< 0.01	98
Study design				
Retrospective	10	23.8 (18.2–30.4)	< 0.01	97
Prospective	7	30.5 (26.1–35.2)	< 0.01	85
Included hospital				
Single center	11	24.8 (17.3–34.3)	< 0.01	96
Multicenter	6	28.1 (25.7–30.7)	< 0.01	80
Septic shock				
28- or 30-day mortality				
Sepsis criteria				
Sepsis-3	16	27.6 (22.3–33.5)	< 0.01	98
Other	15	22.6 (18.8–26.8)	< 0.01	95
Study design				
Retrospective	13	28.0 (21.1–36.0)	< 0.01	98
Prospective	17	23.4 (20.1–27.0)	< 0.01	95
Randomized controlled trial	1	18.0 (11.9–26.3)	-	-
Included hospital				
Single center	22	24.8 (19.8–30.7)	< 0.01	98
Multicenter	9	26.0 (22.7–29.6)	< 0.01	93
In-hospital mortality				
Sepsis criteria				
Sepsis-3	12	34.3 (27.2–42.2)	< 0.01	97
Other	6	26.0 (19.4–33.9)	< 0.01	95
Study design				
Retrospective	6	34.1 (21.1–50.2)	< 0.01	99
Prospective	10	29.8 (25.4–34.7)	< 0.01	93
Randomized controlled trial	2	29.6 (15.8–48.6)	< 0.01	86
Included hospital				
Single center	11	33.3 (24.2–44.0)	< 0.01	97
Multicenter	7	28.6 (23.8–34.1)	< 0.01	94

CI, confidence interval.

<sup>a)</sup>For heterogeneity.

## Statistical analysis

Individual and pooled statistics were calculated as frequencies of sepsis and septic shock diagnosed at admission or during an ICU

stay to estimate mortality in the ICU or hospital and to estimate mortality at 28 or 30 days. A random effects model was used to assess mortality for each outcome. Separate analyses were performed in the following subgroups: diagnosed according to Sepsis-3 and non-Sepsis-3 criteria; retrospective and prospective studies; single-center and multicenter studies; and patient location (emergency room, ward, or ICU). Statistical heterogeneity was visually assessed using forest plots and formally assessed using  $I^2$ . Publication bias was evaluated using a Begg funnel plot. All analyses were performed using the R ver. 4.0.0 (The R Foundation for Statistical Computing) software packages "meta" (ver. 6.1-0) and "metafor" (ver. 3.8-1). A P-value of  $<0.05$  was considered statistically significant.

## RESULTS

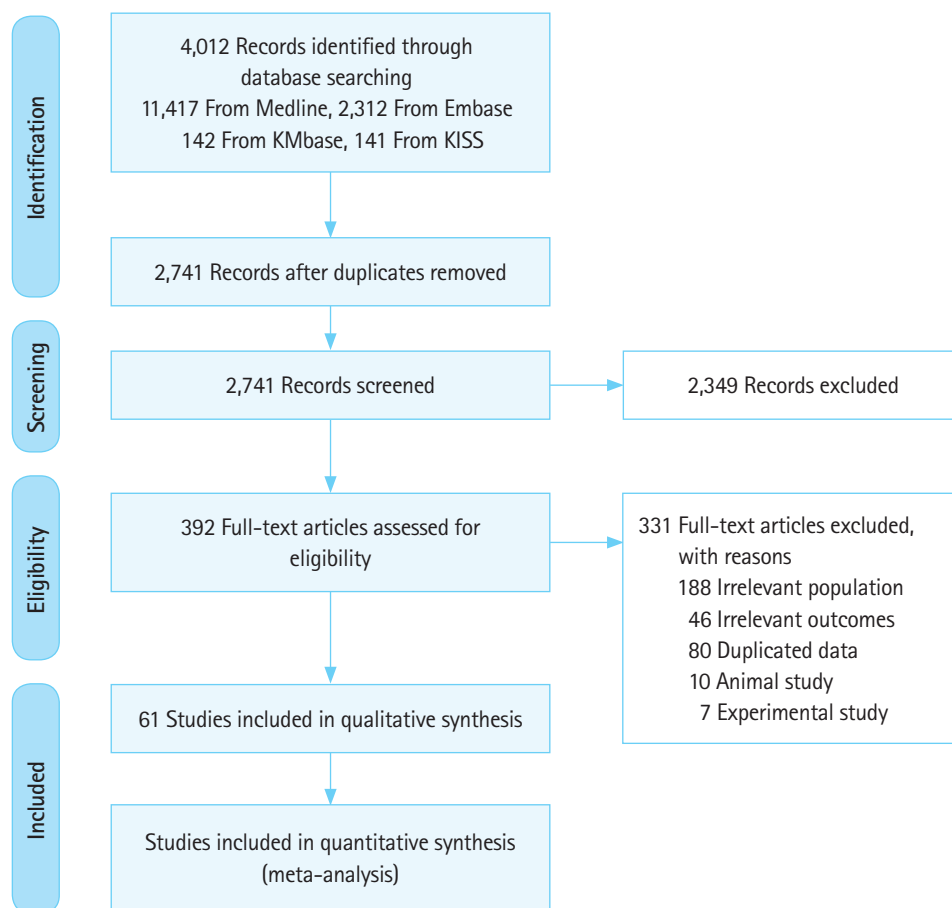
### Study selection

Our database search yielded 4,012 records. From them, 1,271 duplicates were removed, and 2,349 records were excluded in the review of titles and abstracts. Of the remaining 392 records, 331

were also excluded based on the full article review because they had an irrelevant population ( $n=188$ ), irrelevant outcome ( $n=46$ ), duplicated data ( $n=80$ ), animal study ( $n=10$ ), or experimental study ( $n=7$ ); details are provided in Supplementary Tables 2 and 3 [15–75]. Therefore, 61 studies of sepsis and septic shock mortality are included in this review [15–75]. Fig. 1 shows the study flow for the selection process.

### Study characteristics

Of the 61 included studies, 26 were prospective cohort studies, 33 were retrospective cohort studies, and two were randomized clinical trials; 46 were single-center studies, and 15 were multicenter studies, nine of which investigated the same two prospective sepsis registries (five used the Korean Shock Society [KoSS] registry [48,50,52,67,75] and four used the Korean Sepsis Alliance [KSA] registry [28,33,59,73]). The KoSS registry was established in 2013 to study patients who went into septic shock in emergency departments (EDs); it has been prospectively collecting data since October 2015 [76]. At the beginning of enrollment, 10 EDs participated, but in the most recent study, which used data up to



**Fig. 1.** Flowchart for included studies. KMBASE, Korean Medical Database; KISS, Korean Studies Information Service System.

December 2019, 12 EDs participated [48]. The KSA registry was organized mainly by pulmonologists and critical care medicine physicians from 16 secondary and tertiary hospitals nationwide; this database covers 19 hospitals and includes patients who were diagnosed with sepsis in EDs or hospitals [28].

Data on 28- or 30-day mortality and in-hospital mortality among sepsis patients were extracted from 27 and 17 studies, respectively, and those data for septic shock patients were extracted from 32 and 18 studies, respectively. Table 1 summarizes the characteristics of the included studies [15–75].

### Sepsis mortality

The studies that examined 28- or 30-day mortality from sepsis analyzed 22,050 patients. The 28- or 30-day mortality from sepsis diagnosed using the Sepsis-3 criteria was 22.7% (95% confidence interval [CI], 20.0%–25.6%;  $I^2 = 89\%$ ) (Table 2 and Fig. 2) [15,17,21,26,27,35,39,42,46,50,55–59,69,72]. The range of mortality in the included studies was 14.4% to 40.8%. In addition, the 28- or 30-day mortality rate by including all sepsis criteria was 24.8% (95% CI, 22.1%–27.7%;  $I^2 = 95\%$ ) (Supplementary Fig. 1) [15–17,20,21,26,27,29–31,34,35,39,42,44,46,50,55–59,63,69,71,72,74]. In the subgroup analyses, 28- or 30-day mortality from sepsis was 22.6% (95% CI, 19.5%–25.9%;  $I^2 = 94\%$ ) in retrospective cohort studies, 29.1% (95% CI, 23.4%–35.5%;  $I^2 = 96\%$ ) in prospective studies, 23.3% (95% CI, 20.5%–26.5%;  $I^2 = 93\%$ ) in single-center studies, and 31.3% (95% CI, 23.4%–40.4%;  $I^2 = 98\%$ ) in multicenter studies (Table 2).

The studies of in-hospital mortality from sepsis analyzed 11,595

patients. In-hospital mortality from sepsis diagnosed using the Sepsis-3 criteria was 28.1% (95% CI, 25.2%–31.1%;  $I^2 = 87\%$ ) (Table 2 and Fig. 3) [15,17,26–28,32,33,39,41,47,50,59,72]. The range of mortality was 15.7% to 47.0%. In addition, in-hospital mortality by including all sepsis criteria was 26.3% (95% CI, 22.6%–30.5%;  $I^2 = 95\%$ ) (Supplementary Fig. 2) [15,17,26–28,32,33,39,41,44,47,50,59,63,68,70,72]. In the subgroup analyses, the in-hospital mortality from sepsis was 23.8% (95% CI, 18.2%–30.4%;  $I^2 = 97\%$ ) in retrospective cohort studies, 30.5% (95% CI, 26.1%–35.2%;  $I^2 = 85\%$ ) in prospective studies, 24.8% (95% CI, 17.3%–34.3%;  $I^2 = 96\%$ ) in single-center studies, and 28.1% (95% CI, 25.7%–30.7%;  $I^2 = 80\%$ ) in multicenter studies (Table 2).

### Septic shock mortality

The studies for 28- or 30-day mortality from septic shock analyzed 25,101 patients. The 28- or 30-day mortality from septic shock diagnosed using the Sepsis-3 criteria was 27.6% (95% CI, 22.3%–33.5%;  $I^2 = 98\%$ ) (Table 2 and Fig. 4) [15,17,25–27,42,46,48–50,58,60,67,69,73,75]. The range of mortality was 12.6% to 52.9%. In addition, the 28- or 30-day mortality rate by including all sepsis criteria from septic shock was 25.1% (95% CI, 21.8%–28.8%;  $I^2 = 97\%$ ) (Supplementary Fig. 3) [15–17,19,24–27,29,36–38,42,46,48–51,53,54,58,60–62,65–67,69,73–75]. In the subgroup analyses, the 28- or 30-day mortality from septic shock was 28.0% (95% CI, 21.1%–36.0%;  $I^2 = 98\%$ ) in retrospective cohort studies, 23.4% (95% CI, 20.1%–27.0%;  $I^2 = 95\%$ ) in prospective studies, 18.0% in the one randomized controlled trial, 24.8% in single-center studies (95% CI, 19.8%–30.7%;  $I^2 = 98\%$ ), and 26.0% in

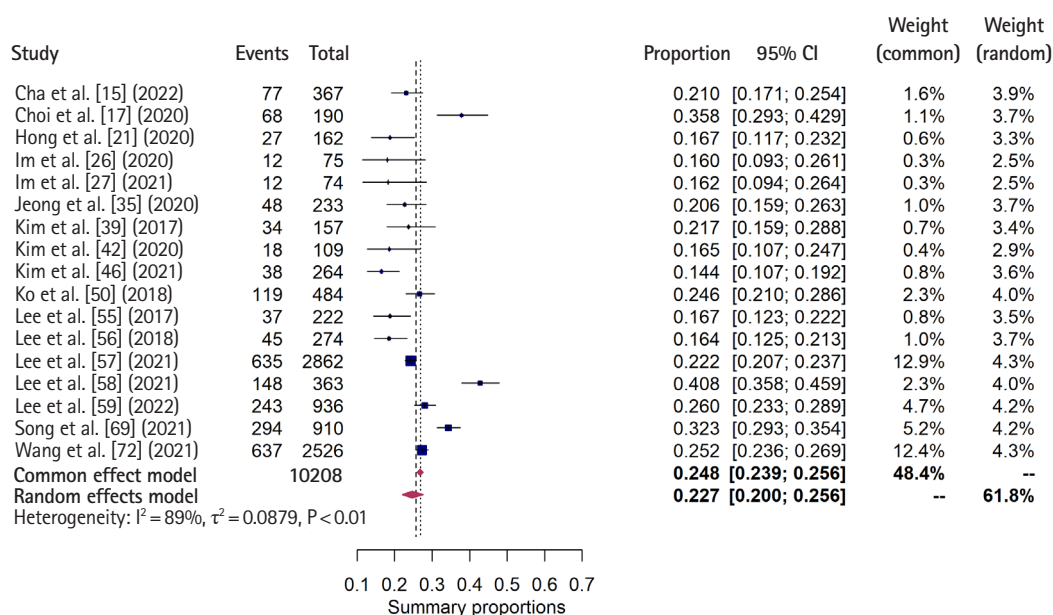


Fig. 2. Forest plot for 28- or 30-day mortality from sepsis using the Sepsis-3 criteria. CI, confidence interval.

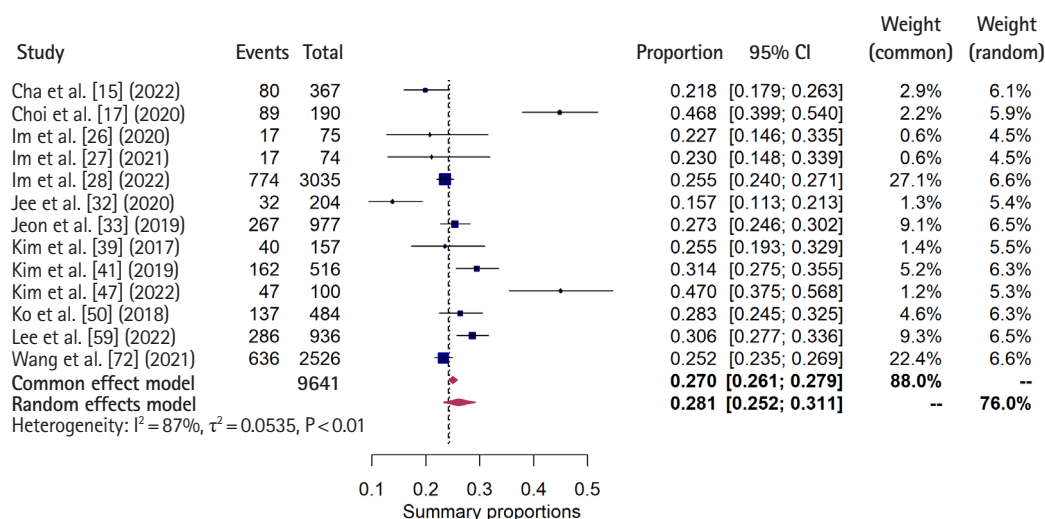


Fig. 3. Forest plot for in-hospital mortality from sepsis using the Sepsis-3 criteria. CI, confidence interval.

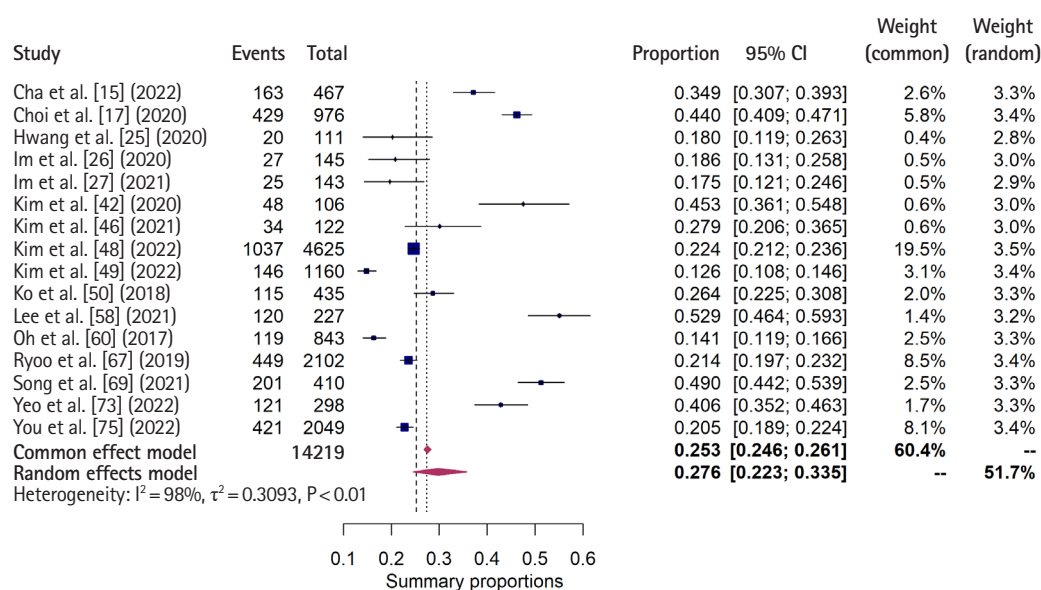


Fig. 4. Forest plot for 28- or 30-day mortality from septic shock using the Sepsis-3 criteria. CI, confidence interval.

multicenter studies (95% CI, 22.7%–29.6%;  $I^2 = 93\%$ ) (Table 2).

The studies of in-hospital mortality from septic shock analyzed 10,769 patients. In-hospital mortality from septic shock diagnosed using the Sepsis-3 criteria was 34.3% (95% CI, 27.2%–42.2%;  $I^2 = 97\%$ ) (Table 2 and Fig. 5) [15,18,25–27,40,45,47,50,52,73,75]. The range of mortality was 21.6% to 50.0%. In addition, in-hospital mortality by including all sepsis criteria from septic shock was 31.4% (95% CI, 26.1%–37.3%;  $I^2 = 97\%$ ) (Supplementary Fig. 4) [15,18,22,23,25–27,37,40,43,45,47,50,52,62,64,73,75]. In the subgroup analyses, the in-hospital mortality from septic shock was 34.1% (95% CI, 21.1%–50.2%;  $I^2 = 99\%$ ) in retrospective cohort studies, 29.8% (95% CI, 25.4%–34.7%;  $I^2 = 93\%$ ) in prospective studies, 29.6% (95% CI, 15.8%–48.6%;  $I^2 = 86\%$ ) in randomized

controlled trials, 33.3% (95% CI, 24.2%–44.0%;  $I^2 = 97\%$ ) in single-center studies, and 28.6% (95% CI, 23.8%–34.1%;  $I^2 = 94\%$ ) in multicenter studies (Table 2).

### Quality assessment

When we used the Newcastle-Ottawa Scale to evaluate the quality of the included articles, we found that 19 studies were of poor quality. The following assessments were derived from the other studies, which were rated as good quality: 24 studies received 9 points, and the others received 7 or 8 points. Using the Risk of Bias 2 for the two randomized controlled trials, one study had low bias, and the other study had high bias (Supplementary Tables 2, 3).

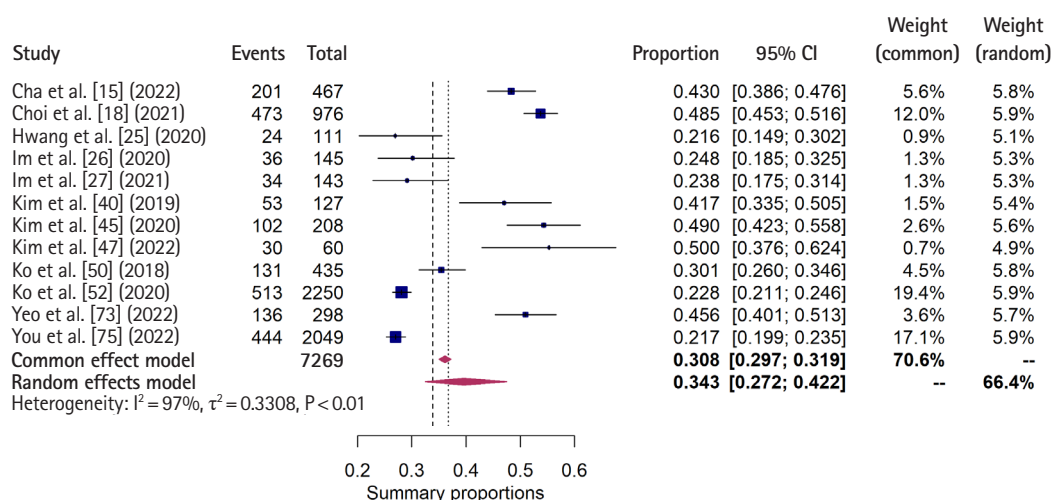


Fig. 5. Forest plot for in-hospital mortality from septic shock using the Sepsis-3 criteria. CI, confidence interval.

### Publication bias

All the funnel plots made to assess the publication bias for each outcome showed symmetry. The funnel plots for sepsis (28- or 30-day and in-hospital mortality) and septic shock (28- or 30-day and in-hospital mortality) are shown in Supplementary Fig. 5.

## DISCUSSION

To the best of our knowledge, this is the first meta-analysis to investigate mortality among sepsis and septic shock patients in Korea. We found that the pooled mean of the 28- or 30-day mortality rate and in-hospital mortality rate are 24.8% and 26.3%, respectively, in sepsis patients, and 25.1% and 31.4%, respectively, in septic shock patients. Those data reflect the actual clinical prognosis of sepsis patients classified according to the sepsis criteria used in hospitals. The 28- or 30-day sepsis mortality rate in a national cohort study by Oh et al. [77] is higher than our result at approximately 30%. However, that study used National Health Insurance Service of Korea data and ICD-10 codes to classify sepsis patients; therefore, the diagnosis of sepsis might have been overestimated by including septic shock. Moreover, deaths unrelated to sepsis might have been included in the overall mortality data of that study.

The sepsis mortality rates in the present study are higher than those reported in a recent meta-analysis for the United States (19.6%) and Australia (18.7%), but similar to that in Europe (23.6%) and lower than that in China (29.1%) [6,7]. In contrast, the mortality rate among septic shock patients appears to be similar or lower than that in other countries (North America, 33.7%; Australia, 26.4%; Europe, 32.5%; China, 35.9%) [6,7]. Most of the sepsis studies evaluated in our meta-analysis included sepsis with

shock, introducing the possibility of heterogeneity among studies and inaccurately high death rates. In addition, because our study includes research from the past 10 years, our data are based on several sets of sepsis criteria (Sepsis-1, -2, and -3), and that inconsistency could increase heterogeneity. On the other hand, we found clinically relevant results when the Sepsis-3 criteria were used.

Another finding of this study is that in-hospital mortality was higher than 28- or 30-day mortality in sepsis and septic shock patients. This result is consistent with that of previous meta-analyses conducted by Vincent et al. [78] and Liu et al. [7] in Europe, North America, and China. The studies included in this meta-analysis presented their outcomes as either 28- or 30-day mortality or in-hospital mortality, and the study populations differed in their inclusion of sepsis or septic shock patients. In other words, 28- or 30-day mortality and in-hospital mortality were not measured consecutively in the same studies but represent the sum of values extracted from different studies. Therefore, because of the statistical constraints of a meta-analysis, caution is needed in interpreting the result that in-hospital mortality was higher than 28- or 30-day mortality in sepsis and septic shock patients.

We analyzed the mortality rates from sepsis and septic shock after dividing the patients into those diagnosed with the Sepsis-3 criteria and those diagnosed with other criteria. The 28- or 30-day mortality rate and in-hospital mortality rates for septic shock diagnosed according to the Sepsis-3 criteria were 27.6% and 34.3%, respectively, which are higher than those based on the non-Sepsis-3 criteria (28- or 30-day mortality, 22.6%; in-hospital mortality, 26.0%) (Figs. 4, 5) [15,17,18,25-27,40,42,45-50,52,58,60,67,69,73,75]. That finding is consistent with a previous meta-

analysis in Europe and North America, which reported that in-hospital septic shock mortality increased significantly, from 39.0% to 52.1%, when the Sepsis-3 criteria were used for diagnosis [78]. The criteria prior to Sepsis-3 defined sepsis as a state with at least two of the four systemic inflammatory response syndrome (SIRS) criteria, which focus solely on the inflammatory response [79,80]. Because the SIRS criteria do not exactly reflect organ dysfunction and life-threatening conditions, the new Sepsis-3 criteria, which were published in 2016, include the Sequential Organ Failure Assessment (SOFA) score and lactate level [1]. Therefore, the increase in septic shock mortality when using the Sepsis-3 criteria could be explained by the advanced disease severity reflected by the change in diagnostic criteria.

Variations in mortality rates among the included studies are likely attributable to differences in the disease severity of the patients. For example, to identify the risk factors of sepsis-associated delirium and their effects on the outcomes of ICU patients, Kim et al. [44] excluded patients with <24 hours of ICU stay or deep or full sedation from their assessment of 28- or 30-day sepsis mortality. Those factors could exacerbate the severity of the patients included, resulting in a higher mortality rate. In addition, Hong et al. [20] excluded patients admitted for hemodialysis or peritoneal dialysis, transferred from other hospitals, or admitted for palliative care. In that case, the mortality rate might have been underreported due to the exclusion of critically ill patients. It is challenging to generalize the findings of this study to all sepsis patients in Korea. The majority of the research included in this meta-analysis was conducted at tertiary medical institutions or large hospitals, and the sepsis registries include only hospitals with the ability to provide quality care. Thus, data from institutions that are treating sepsis but not reporting their results were not included here. If the outcomes from ineffective-performance medical settings are not considered, the overall results of sepsis treatment might appear to be better than they actually are. Additionally, a recent Korean report indicated that the surviving sepsis campaign had low compliance [81]. Therefore, the mortality rate might increase further when the sepsis outcomes of all medical institutions are considered. Further investigation is needed to examine sepsis outcomes according to the performance level of the medical institution.

This review has several limitations. First, heterogeneity among the studies included in the meta-analysis is very high, all over 95%. One reason for this high heterogeneity is the diversity of study designs included in the analysis. In addition, the definition of sepsis in the included studies was heterogeneous because the new Sepsis-3 criteria were only published in 2016, and that diversity of definitions might have resulted in a wide range of mor-

tality rates. Therefore, we analyzed the mortality rates according to the use of the Sepsis-3 and non-Sepsis-3 criteria. Second, the sepsis criteria were met when patients were included in these studies, but it is possible that critically ill patients might have been only selectively included based on particular domains, such as the lactate level. Third, when several studies were conducted in a single institution or used the same registry during the same study period, we selected only the study with the longest study period and largest sample size because we suspected that the study population might be duplicated. Thus, despite our efforts to include as many studies as possible, we cannot completely rule out the possibility of selection bias. Fourth, despite that attempt to prevent duplicated data, the possibility of duplication between registry studies and single-center studies whose data are included in that registry remains. Fifth, the medical history and care conditions of individual patients, which influence the mortality rate, were not considered. Personal factors were not considered in this study, and our meta-analysis simply confirmed the mortality rate.

In conclusion, our study shows that the mortality rates from sepsis and septic shock in Korea are high. In the case of septic shock, the in-hospital mortality rate is approximately 30%, and that rate was higher when septic shock was diagnosed according to the Sepsis-3 criteria than when it was diagnosed using other criteria.

## SUPPLEMENTARY MATERIALS

**Supplementary Table 1.** Search strategy

**Supplementary Table 2.** Quality assessment using Newcastle-Ottawa Scale for cohort studies

**Supplementary Table 3.** Quality assessments using Risk of Bias 2 for randomized controlled trials

**Supplementary Fig. 1.** Forest plot for 28- or 30-day sepsis mortality by including all sepsis criteria.

**Supplementary Fig. 2.** Forest plot for in-hospital sepsis mortality by including all sepsis criteria.

**Supplementary Fig. 3.** Forest plot for 28- or 30-day septic shock mortality by including all sepsis criteria.

**Supplementary Fig. 4.** Forest plot for in-hospital septic shock mortality by including all sepsis criteria.

**Supplementary Fig. 5.** Funnel plots for each outcome.

Supplementary materials are available from <https://doi.org/10.15441/ceem.23.005>.

## ETHICS STATEMENTS

Not applicable.

## CONFLICT OF INTEREST

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

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None.

## AUTHOR CONTRIBUTIONS

Conceptualization: MN, CA; Data curation: MN, YP, MW; Formal analysis: IYK, JL; Visualization: CA; Writing—original draft: MN, CA; Writing—review & editing: all authors. All authors read and approved the final manuscript.

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Supplementary Table 1. Search strategy

Database	Search strategy	No. of studies
Medline	septic shock/ OR sepsis/ OR ((bacteremic OR bacterial OR bacteriemic OR endotoxic OR endotoxine OR toxic) AND shock) AND epidem*.ti,ab,kw OR frequen*.ti,ab,kw OR prevalence.ti,ab,kw. OR incidence.ti,ab,kw OR mortality.ti,ab,kw AND Korea/ OR South Korea/ OR korea*	1,417
Embase	'septic shock'/exp OR 'septic shock' OR 'sepsis' OR ((bacteremic OR bacterial OR bacteriemic OR endotoxic OR endotoxine OR toxic) AND shock) AND epidem*:ab,kw,ti OR frequen*:ab,kw,ti OR incidence:ab,kw,ti OR 'prevalence' OR 'prevalence' AND 'south korea' OR 'korea' OR korea*:ab,kw,ti	2,312
KoreaMed	((("septic shock"[ALL]) OR ("sepsis"[ALL]) OR ("bacteremic"[ALL]) OR (((("bacterial"[ALL]) OR ("bacteriemic"[ALL]))) AND ("shock"[ALL])))) AND (("epidem*"[ALL]) OR ("frequen*"[ALL]) OR ("prevalence"[ALL]) OR ("incidence*"[ALL]) OR ("mortality*"[ALL]))	142
KISS	sepsis OR septic shock	141
Total		4,012

KISS, Korean Studies Information Service System.

Supplementary Table 2. Quality assessment using Newcastle-Ottawa Scale for cohort studies

Study	Selection				Comparability	Outcome			Quality power
	Representa- tiveness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis controlled for confounders	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Cha et al. [15] (2022)	★	-	★	★	★	★	★	-	Good
Cho et al. [16] (2012)	★	★	★	★	-	★	★	★	Poor
Choi et al. [17] (2020)	★	-	★	★	-	★	★	★	Poor
Choi et al. [18] (2021)	★	★	★	★	★★	★	★	★	Good
Chung et al. [19] (2019)	★	★	★	★	★★	★	★	★	Good
Hong et al. [20] (2016)	★	★	★	★	★★	★	★	★	Good
Hong et al. [21] (2020)	★	★	★	★	★★	★	★	★	Good
Hwang et al. [23] (2018)	★	★	★	★	-	★	★	★	Poor
Hwang et al. [24] (2019)	★	★	★	★	★	★	★	★	Good
Im et al. [26] (2020)	★	★	★	★	-	★	★	★	Poor
Im et al. [27] (2021)	★	-	★	★	-	★	★	★	Poor
Im et al. [28] (2022)	★	★	★	★	★★	★	★	★	Good
Jang et al. [29] (2016)	★	★	★	★	-	★	★	★	Poor
Jang et al. [30] (2020)	★	★	★	★	★★	★	★	★	Good
Jang et al. [31] (2021)	★	★	★	★	★★	★	★	★	Good
Jee et al. [32] (2020)	★	★	★	★	-	★	★	★	Poor
Jeon et al. [33] (2019)	★	★	★	★	★	★	★	★	Good
Jeong et al. [34] (2019)	★	★	★	★	★★	★	★	★	Good
Jeong et al. [35] (2020)	★	★	★	★	-	★	★	★	Poor
Jung et al. [36] (2019)	★	★	★	★	★★	★	★	★	Good
Kim et al. [37] (2012)	★	★	★	★	★★	★	★	★	Good
Kim et al. [38] (2013)	★	★	★	★	★	★	★	★	Good
Kim et al. [39] (2017)	★	★	★	★	-	★	★	★	Poor
Kim et al. [40] (2019)	★	★	★	★	-	★	★	★	Poor
Kim et al. [41] (2019)	★	★	★	★	★	★	★	★	Good
Kim et al. [42] (2020)	★	-	★	★	-	★	★	★	Poor
Kim et al. [43] (2020)	★	-	★	★	★	★	★	★	Good
Kim et al. [44] (2020)	★	★	★	★	★★	★	★	★	Good
Kim et al. [45] (2020)	★	★	★	★	★★	★	★	★	Good
Kim et al. [46] (2021)	★	-	★	★	-	★	★	★	Poor
Kim et al. [47] (2022)	★	★	★	★	★	★	★	★	Good
Kim et al. [48] (2022)	★	-	★	★	★	★	★	★	Good
Kim et al. [49] (2022)	★	★	★	★	★★	★	★	★	Good
Ko et al. [50] (2018)	★	★	★	★	-	★	★	★	Poor
Ko et al. [51] (2019)	★	★	★	★	★	★	★	★	Good
Ko et al. [52] (2020)	★	★	★	★	-	★	★	★	Poor
Lee et al. [53] (2012)	★	★	★	★	★★	★	★	★	Good
Lee et al. [54] (2013)	★	★	★	★	★★	★	★	★	Good
Lee et al. [55] (2017)	★	★	★	★	★★	★	★	★	Good
Lee et al. [56] (2018)	★	★	★	★	★★	★	★	★	Good
Lee et al. [57] (2021)	★	★	★	★	★★	★	★	★	Good
Lee et al. [58] (2021)	★	-	★	★	★	★	★	★	Good
Lee et al. [59] (2022)	★	★	★	★	★★	★	★	★	Good
Oh et al. [60] (2017)	★	★	★	★	★★	★	★	★	Good
Oh et al. [61] (2019)	★	★	★	★	★	★	★	★	Good
Park et al. [62] (2012)	★	★	★	★	★	★	★	★	Good

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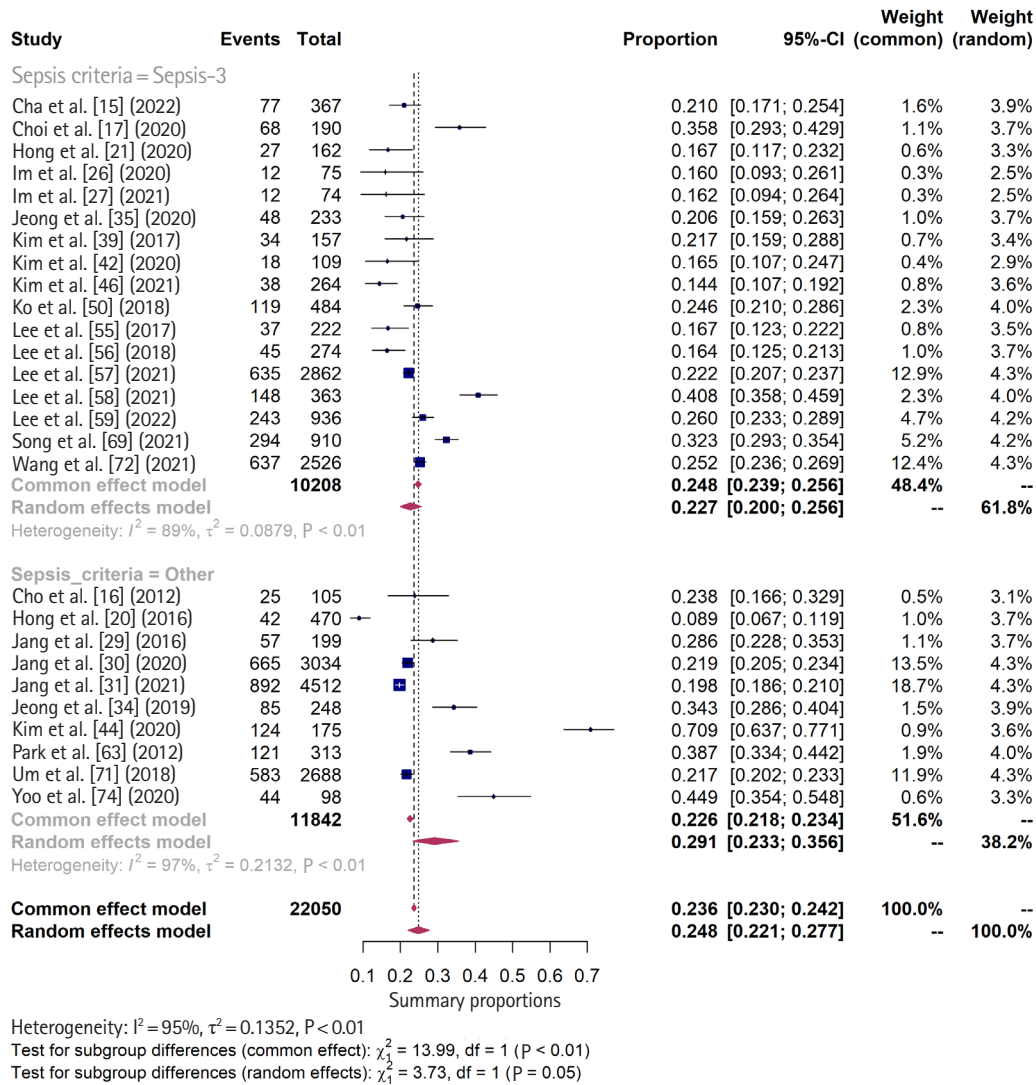
Supplementary Table 2. (Continued)

Study	Selection				Comparability	Outcome			Quality power
	Representa- tiveness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis controlled for confounders	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Park et al. [63] (2012)	★	★	★	★	★	★	★	★	Good
Park et al. [64] (2015)	★	★	★	★	-	★	★	★	Poor
Park et al. [65] (2020)	★	-	★	★	-	★	★	★	Poor
Ryoo et al. [66] (2015)	★	★	★	★	-	★	★	★	Poor
Ryoo et al. [67] (2019)	★	-	★	★	-	★	★	★	Poor
Song et al. [68] (2012)	★	★	★	★	★	★	★	★	Good
Song et al. [69] (2021)	★	★	★	★	★★	★	★	★	Good
Suh et al. [70] (2013)	★	★	★	★	-	★	★	★	Poor
Um et al. [71] (2018)	★	★	★	★	★★	★	★	★	Good
Wang et al. [72] (2021)	★	★	★	★	★★	★	★	★	Good
Yeo et al. [73] (2022)	★	★	★	★	★	★	★	★	Good
Yoo et al. [74] (2020)	★	-	★	★	★	★	★	★	Good
You et al. [75] (2022)	★	★	★	★	★★	★	★	★	Good

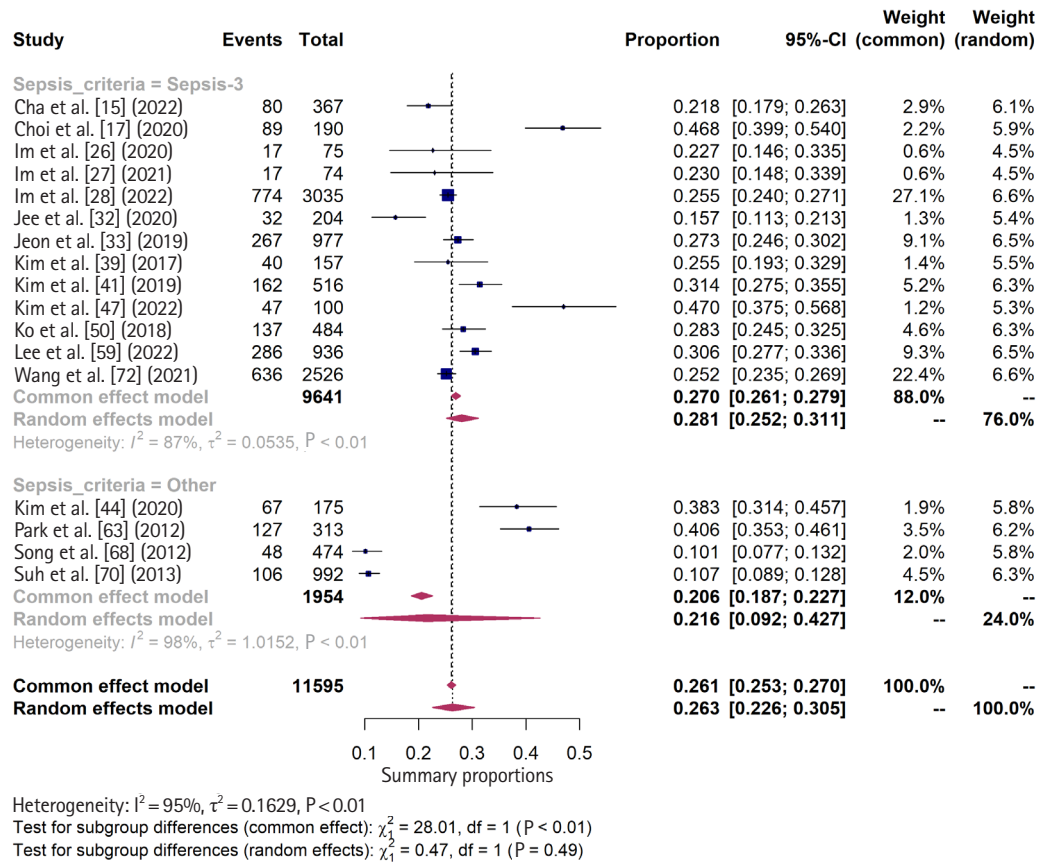
Each article was rated based on selection (maximum, four stars), comparability (maximum, two stars), and outcome (maximum, three stars).

**Supplementary Table 3.** Quality assessments using Risk of Bias 2 for randomized controlled trials

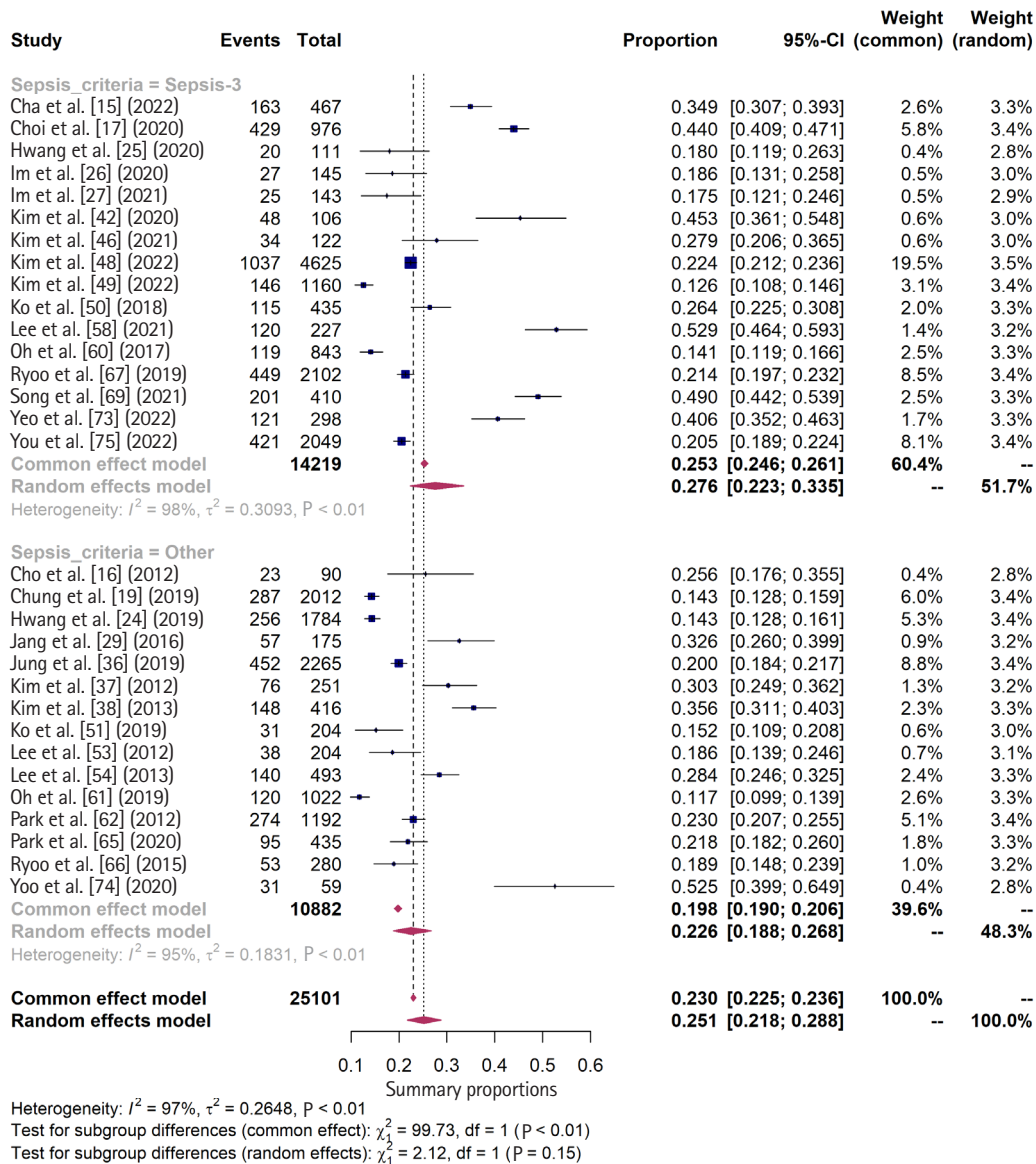
Study	Selection bias	Performance bias	Attrition bias	Detection bias	Reporting bias	Overall
Hwang et al. [25] (2020)	Low	Low	Low	Low	Low	Low
Huh et al. [22] (2013)	Some concerns	Low	Low	High	Low	High



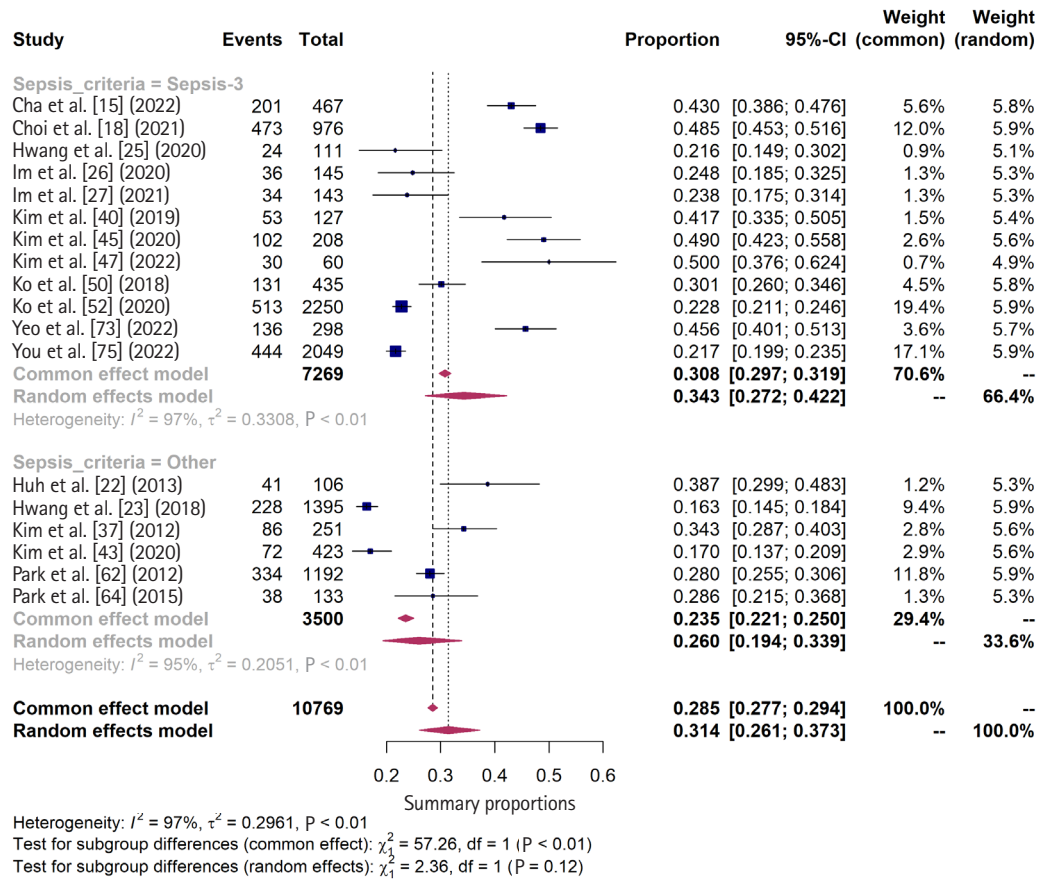
Supplementary Fig. 1. Forest plot for 28- or 30-day sepsis mortality by including all sepsis criteria.



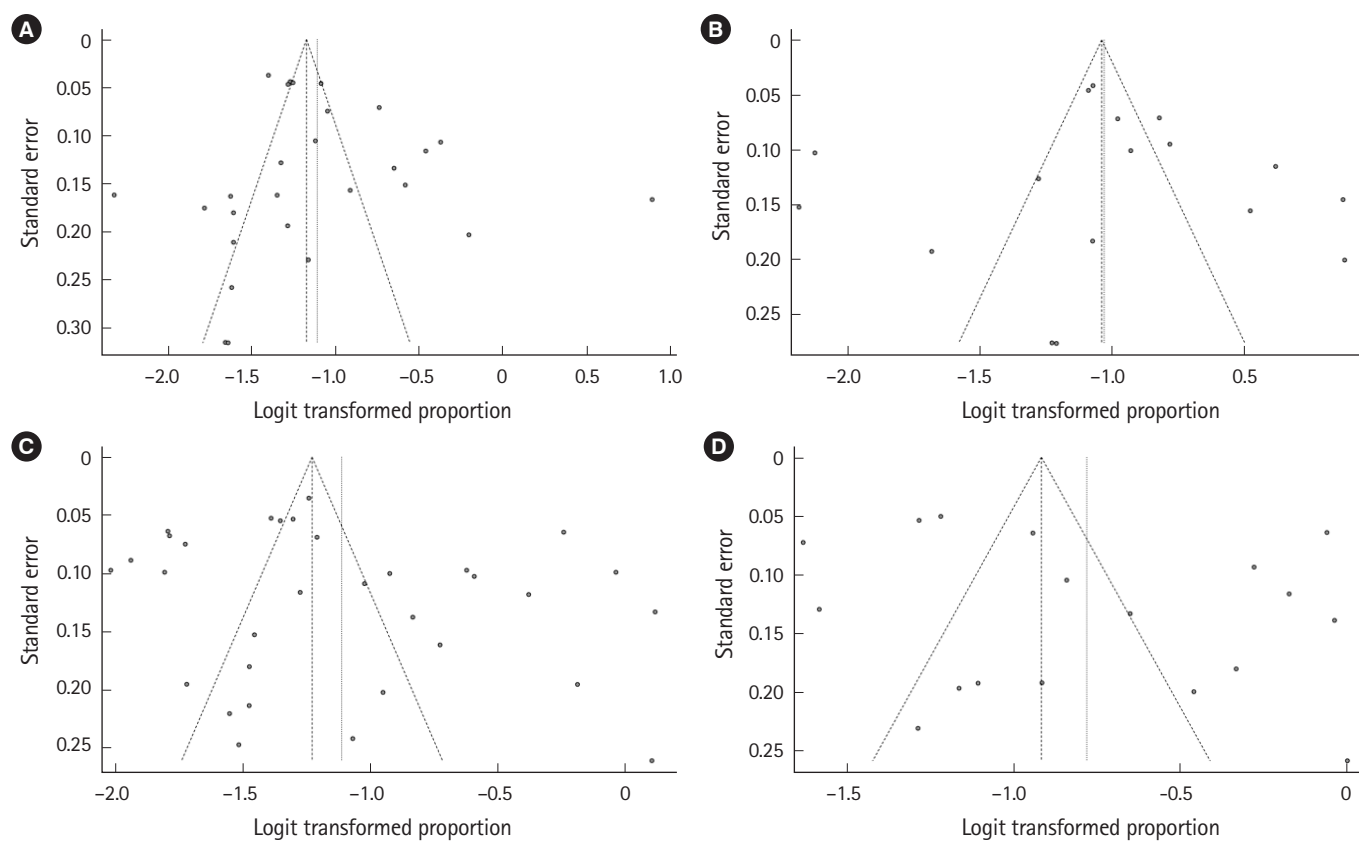
**Supplementary Fig. 2.** Forest plot for in-hospital sepsis mortality by including all sepsis criteria.



Supplementary Fig. 3. Forest plot for 28- or 30-day septic shock mortality by including all sepsis criteria.



Supplementary Fig. 4. Forest plot for in-hospital septic shock mortality by including all sepsis criteria.



**Supplementary Fig. 5.** Funnel plots for each outcome. (A) The 28- or 30-day mortality for sepsis. (B) In-hospital mortality for sepsis. (C) The 28- or 30-day mortality for septic shock. (D) In-hospital mortality for septic shock.

# Hyponatremia and hypernatremia in the emergency department: severity and outcomes

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**Objective** Hyponatremia and hypernatremia are common electrolyte disorders. Few studies to date have focused on patients presenting to the emergency department (ED) with sodium (Na) disorders. Our objective was to determine the incidence and outcomes of hyponatremia and hypernatremia in ED patients.

**Methods** This study was a retrospective, single-center review of electronic medical records at an academic suburban ED with approximately 100,000 annual visits. Subjects included consecutive adult ED patients with Na levels measured while in the ED in 2019. Demographic, clinical, and laboratory data were recorded. Outcomes data, including hospital admission, intensive care unit (ICU) admission, mortality, and length of stay (LOS), were recorded. The primary outcome was in-hospital death. Secondary outcomes were hospital admission, ICU admission, ED LOS, and hospital LOS. Univariable and multivariable linear and logistic regression analyses were performed to explore the association of candidate predictor variables and outcomes.

**Results** Na was measured in 57,427 adults (54%) among a total of 106,764 assessed ED visits in 2019. The mean  $\pm$  standard deviation age was  $54 \pm 21$  years, and 47% of participants were male. Mild, moderate, and severe hyponatremia and hypernatremia occurred in 8%, 2%, and 0.1% of patients and 1%, 0.2%, and  $<0.1\%$  of patients, respectively. Hospital and ICU admission and mortality rates increased as Na levels increased or decreased further from normal. Adjusted odds ratio (95% confidence interval) values for hospital mortality were 2.39 (1.97–2.90) for mild hyponatremia, 3.93 (2.95–5.24) for moderate hyponatremia, 6.98 (2.87–16.40) for severe hyponatremia, 3.65 (2.47–5.40) for mild hypernatremia, 8.58 (4.92–14.94) for moderate hypernatremia, and 55.75 (11.37–273.30) for severe hypernatremia. Hypernatremia was associated with a greater risk of death than hyponatremia. Patients with hyponatremia and hypernatremia had increased LOS times compared to those with normal Na levels.

**Conclusion** Hyponatremia and hypernatremia were associated with greater rates of hospital admission, ICU admission, mortality, and prolonged hospital LOS times.

**Keywords** Hypernatremia; Hyponatremia; Emergency department

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## Capsule Summary

### What is already known

*Hyponatremia and hypernatremia are common electrolyte disorders; however, there is a paucity of research pertaining to outcomes of sodium derangements in emergency department patients.*

### What is new in the current study

*Both hyponatremia and hypernatremia were associated with increased rates of hospital admission, intensive care unit admission, and mortality. Outcomes worsened, and were proportional to, increases or decreases from normal sodium level. Outcomes were worse in hypernatremia compared to hyponatremia. The presence of dysnatremia was associated with increased length of stay.*

## INTRODUCTION

Electrolyte disorders are common in patients presenting to the emergency department (ED). Hyponatremia is the most common electrolyte abnormality observed and is found in approximately 3% to 6% of ED patients [1,2]. Hyponatremia is important to recognize as it has been associated with increased hospital length of stay (LOS) times, increased morbidity or mortality, and increased health care costs [3–7]. Although there are several causes of hyponatremia, some of the more common risk factors include heart failure, chronic kidney disease, hepatic failure, body fluid losses, and disorders that increase the total body water content like the syndrome of inappropriate antidiuretic hormone and adrenal insufficiency.

Hypernatremia is less common than hyponatremia and is uncommon in previously healthy patients, as most cases are due to a total body water deficit from either poor access to water or an impaired thirst mechanism [1]. As such, hypernatremia is more commonly seen in elderly patients and patients with mental or physical impairment. Other risk factors include heat illness, increased fluid losses, excessive salt intake, and disorders that facilitate a reduction in total body water content such as diabetes insipidus. Hypernatremia is associated with increased morbidity and mortality rates among hospitalized patients [8]. One large retrospective study found that, in patients with severe hypernatremia (sodium [Na] > 160 mmol/L), the mortality rate during hospitalization was almost 50% [9].

Although mild cases in asymptomatic patients may not require acute intervention, prompt recognition and treatment are required to prevent the morbidity and mortality associated with more severe cases of hyponatremia and hypernatremia. As the life expectancy in the United States continues to rise [10] and many of the disorders that cause Na abnormalities are common in the elderly, we can expect that hyponatremia and hypernatremia will contin-

ue to place a significant burden on our health care system in the decades to come.

Although Na derangements are common and potentially dangerous, there is a paucity of ED literature. Many of the studies pertaining to Na derangements involve hospitalized or ambulatory care patients [11–13]. Some studies exist that evaluated hyponatremia or hypernatremia not in general ED patients but instead under specific circumstances, such as acute kidney injury [14], sepsis [15], or pneumonia [16]. Other ED-based studies have evaluated risk factors for hyponatremia and hypernatremia, including season and age [17–20]. There are ED-based studies that have compared the severity and outcomes of potassium disturbances [21]; however, our review of the literature did not yield many studies comparing the prevalence and outcomes of hyponatremia and hypernatremia in ED patients.

Our study aims to evaluate the incidence rates of mild, moderate, and severe hyponatremia and hypernatremia amongst ED patients and to compare the outcomes across those groups. We also explored the association of predictor variables and outcomes. Lastly, we examined the impact of Na derangement on ED and total hospital LOS. This study is unique in that it directly compares the mortality rates of hyponatremia and hypernatremia in ED patients.

## METHODS

### Ethics statements

As a retrospective chart review, the requirement for informed consent was waived.

### Study design, setting, and patients

This study was a structured, retrospective review of electronic medical records for consecutive adult ED patients with Na levels measured while in the ED in 2019. All adult patients (> 18 years

of age) who had a Na level measured were included. There were no exclusion criteria other than adult patients without a Na level measurement. This was a single-center study that took place at a tertiary care, level I trauma center, which is an academic suburban ED located in Long Island, NY, USA, with approximately 100,000 annual visits.

### Data collection and laboratory testing

Demographic, clinical, and laboratory data were recorded. Na was measured using a Cobas c501 analyzer (Roche), with a normal range defined as 130 to 145 mEq/L. Hyponatremia was defined as mild, moderate, and severe at <130–134, 120–129, and <120 mEq/L, respectively. Mild, moderate, and severe hypernatremia were defined as 146–149, 150–169, and >170 mEq/L, respectively. The mortality rate was defined by the number of deaths that occurred in the hospital.

### Outcomes

Our primary outcome was in-hospital death. Secondary outcomes were hospital admission, intensive care unit (ICU) admission, ED LOS, and hospital LOS.

### Data analysis

We used descriptive statistics to summarize the data. Binary and categorical data are presented as numbers and percentages fre-

quencies of occurrence and compared across groups with the chi-squared or Fisher exact test as appropriate. Continuous data are presented as means and standard deviations or medians and interquartile ranges. Univariable analysis and multivariable linear regression were used to compare outcomes by Na level and are presented as adjusted odds ratios (aORs). Multivariable models adopted linear regression for LOS data and logistic regression for admission, ICU, and mortality data, with coefficients for the former and ORs for the latter. Multivariable outcome predictors, including sex, age, and the presence and severity of dysnatremia, were analyzed, and ORs were calculated to determine the impact on hospital admission, ICU admission, and mortality. Coefficients were calculated for various LOS predictors, including age, sex, Na level, and Charlson Comorbidity Index (CCI). All analyses were conducted using IBM SPSS ver. 27 (IBM Corp).

## RESULTS

A total of 106,764 ED visits occurred in 2019 and, during these visits, Na was measured in 57,427 adults (54%). Forty-six percent of these patients were male, and their mean  $\pm$  standard deviation age was  $54 \pm 21$  years. The mean CCI was  $1.4 \pm 1.8$  points. A summary of results is presented in Table 1.

As seen in Table 2, mild, moderate, and severe hyponatremia occurred in 8%, 2%, and 0.1% of patients, respectively, while mild, moderate, and severe hypernatremia occurred in 1%, 0.2%, and <0.1% of patients. For mild and moderate hyponatremia, rates were similar in men and women (49% vs. 51%); however, we found a female sex predominance in the group of patients with severe hyponatremia (64% female vs. 36% male). In the mild and moderate hypernatremia groups, we found a slight male predominance; conversely, 57% of the cases of severe hypernatremia were observed in women. The mean age was higher in patients with hyponatremia compared to normal Na levels. The mean age was also higher in patients with hypernatremia compared to normal Na levels, with the most drastic difference observed in the

**Table 1.** Demographic data and the incidence of sodium disturbance (n=57,427)

Variable	Value
Age (yr)	$54 \pm 21$
Male sex (%)	26,990 (47)
Charlson comorbidity Index	$1.4 \pm 1.8$
Sodium level	
Hyponatremic	5,512 (10)
Normal	51,193 (89)
Hypernatremic	722 (1)

Values are presented as mean  $\pm$  standard deviation or number (%).

**Table 2.** Demographic data according to the severity of hyponatremia and hypernatremia (n=57,427)

Variable	Hyponatremia			Normal Na level	Hypernatremia		
	Mild	Moderate	Severe		Mild	Moderate	Severe
No. of cases	4,412 (8)	1,028 (2)	72 (0.1)	51,193 (89)	603 (1)	112 (0.2)	7 (<0.1)
Sex							
Male	2,179 (49)	505 (49)	26 (36)	23,560 (46)	321 (53)	60 (54)	3 (43)
Female	2,233 (51)	523 (51)	46 (64)	27,633 (54)	282 (47)	52 (46)	4 (57)
Age (yr)	$61 \pm 19$	$65 \pm 17$	$65 \pm 16$	$53 \pm 21$	$61 \pm 21$	$69 \pm 22$	$82 \pm 15$
CCI	$2.1 \pm 2.0$	$2.2 \pm 2.1$	$1.7 \pm 1.8$	$1.3 \pm 1.7$	$1.4 \pm 1.7$	$1.9 \pm 1.6$	$1.7 \pm 1.6$

Values are presented as number (%) or mean  $\pm$  standard deviation. Na, sodium; CCI, Charlson Comorbidity Index.

severe hyponatremia category (mean age, 82 years vs. 53 years for the normal Na population). The mean CCI score was higher in all groups of hyponatremia and hypernatremia compared to pa-

**Table 3.** Multivariable predictors of outcomes

Predictor	Odds ratio	95% Confidence interval
<b>Admission</b>		
Sex		
Male	Reference	
Female	0.90	0.87–0.93
Age	1.02	1.02–1.03
Na level		
Normal	Reference	
Hyponatremia		
Mild	2.01	1.88–2.15
Moderate	4.87	4.14–5.73
Severe	16.88	6.75–42.23
Hypernatremia		
Mild	1.50	1.27–1.78
Moderate/severe <sup>a)</sup>	6.43	3.79–10.89
CCI	1.21	1.19–1.22
<b>Intensive care unit (admitted only)</b>		
Sex		
Male	Reference	
Female	0.79	0.74–0.84
Age	1.00	0.99–1.00
Na level		
Normal	Reference	
Hyponatremia		
Mild	1.06	0.96–1.16
Moderate	1.18	1.01–1.39
Severe	3.35	2.07–5.42
Hypernatremia		
Mild	0.91	0.69–1.18
Moderate	1.20	0.76–1.90
Severe	1.39	0.27–7.20
CCI	0.95	0.94–0.98
<b>Mortality</b>		
Sex		
Male	Reference	
Female	0.70	0.60–0.81
Age	1.05	1.04–1.05
Na level		
Normal	Reference	
Hyponatremia		
Mild	2.39	1.97–2.90
Moderate	3.93	2.95–5.24
Severe	6.98	2.87–16.40
Hypernatremia		
Mild	3.65	2.47–5.40
Moderate	8.58	4.92–14.94
Severe	55.75	11.37–273.30
CCI	1.03	0.99–1.07

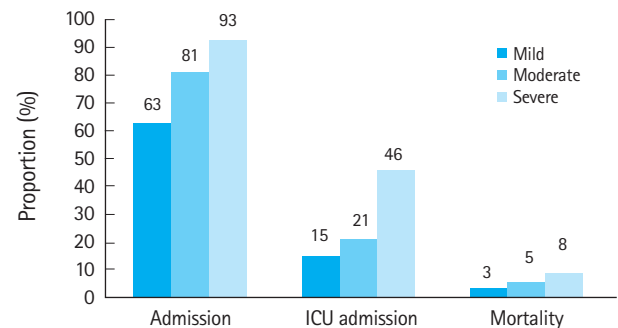
Na, sodium; CCI, Charlson Comorbidity Index.

<sup>a)</sup>The severe hypernatremia group was combined with the moderate hypernatremia group due to the 0 nonadmissions in the former group.

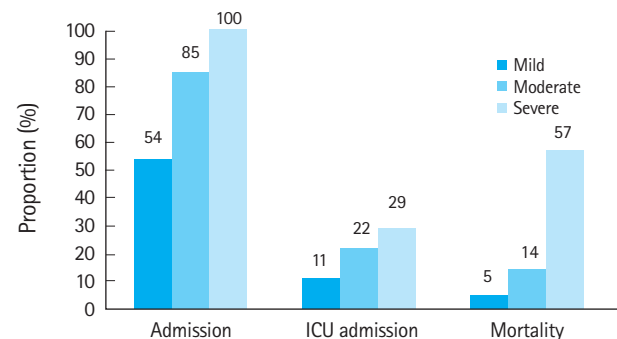
tients with normal Na levels.

Outcome data are summarized in Table 3 and Figs. 1 and 2. Admission, ICU admission, and mortality rates increased as Na levels increased or decreased further from normal. Hypernatremia was associated with a greater risk of death than hyponatremia. Compared to patients with normal Na levels, the aOR (95% confidence interval [CI]) values of mortality in patients with hyponatremia were as follows: mild, 2.39 (1.97–2.90); moderate, 3.93 (2.95–5.24); and severe, 6.98 (2.87–16.40). In comparing the hypernatremia group to patients with normal Na levels, the aOR (95% CI) values of mortality were as follows: mild, 3.65 (2.47–5.40); moderate, 8.58 (4.92–14.94); and severe, 55.75 (11.37–273.30). Age (aOR, 1.048; 95% CI, 1.043–1.053) and female sex (aOR, 0.70; 95% CI, 0.60–0.81) were also associated with mortality, and the CCI was associated with admission rate (aOR, 1.21; 95% CI, 1.19–1.22).

LOS data are reported in Table 4. Multivariable linear regression was used to analyze the data. Coefficients indicate the increased number of LOS hours if the factor is present. Stepwise linear regression was performed with potential predictors such as age, sex, Na level, and CCI. Patients with moderate and severe hyper-



**Fig. 1.** Severity of hyponatremia and patient outcomes.  $P < 0.001$  for all outcomes. ICU, intensive care unit.



**Fig. 2.** Severity of hypernatremia and patient outcomes.  $P < 0.001$  for admissions,  $P = 0.004$  for intensive care unit (ICU) admissions, and  $P < 0.001$  for mortality.

Table 4. LOS predictors

Predictor	Coefficient	95% Confidence interval
Total LOS (ED discharges and admits) <sup>a)</sup>		
Age (per yr)	0.9	0.8–1.0
Sex		
Female	Reference	
Male	18.0	14.4–21.5
CCI (per point)	8.8	7.7–9.9
Na level		
Normal	Reference	
Hyponatremia		
Mild	38.3	31.6–45.0
Moderate	86.9	73.4–100.5
Severe	169.2	117.8–220.6
Hypernatremia		
Mild	56.9	39.3–74.4
Moderate/severe <sup>b)</sup>	112.6	70.6–154.6
Total LOS (admits only) <sup>a)</sup>		
Age (per yr)	0.4	0.2–0.6
Sex		
Female	Reference	
Male sex	33.8	25.7–41.8
CCI (per point)	4.9	2.8–7.1
Na level		
Normal	Reference	
Hyponatremia		
Mild	29.6	16.8–42.4
Moderate	55.1	32.6–77.5
Severe	112.5	34.6–190.4
Hypernatremia		
Mild	84.2	48.2–120.1
Moderate/severe <sup>b)</sup>	70.7	4.0–137.4
ED LOS (nonadmits only) <sup>a)</sup>		
Age (per yr)	0.03	0.03–0.04
Sex		
Female	Reference	
Male	0.9	0.6–1.1
CCI (per point)	0.2	0.1–0.2
Na level		
Normal	Reference	
Hyponatremia		
Mild	1.1	0.6–1.6
Moderate	2.6	1.2–3.9
Severe	11.3	0.5–22.1
Hypernatremia		
Mild	3.7	2.6–4.9
Moderate/severe <sup>b)</sup>	6.6	1.5–11.8

LOS, length of stay; ED, emergency department; CCI, Charlson Comorbidity Index; Na, sodium.

<sup>a)</sup>Excludes deaths. <sup>b)</sup>Cases of moderate and severe hypernatremia were combined due to the small number of severe cases.

natremia were combined into a single group due to the small number of severe cases. For all calculated LOS data, increased age led

to increased LOS times. Excluding deaths, for the total LOS (ED discharges and admissions), male sex and CCI were associated with greater LOS times with coefficients of 18.0 and 8.8, respectively. All severities of hyponatremia and hypernatremia increased the LOS, and the increase in LOS was proportional to the degree of Na derangement, with the largest coefficients seen in severe hyponatremia (169.2) and moderate/severe hypernatremia (112.6). Total LOS data for admitted patients showed similar yet less drastic trends, with male sex (coefficient, 33.8), CCI (coefficient, 4.9), and Na derangement (severe hyponatremia coefficient, 112.5; moderate hyponatremia coefficient, 55.1; mild hyponatremia coefficient, 29.6; mild hypernatremia coefficient, 84.2; moderate/severe hypernatremia coefficient, 70.7) leading to increased LOS times. For ED LOS, similar associations were found, yet the effect of all predictors on ED LOS was smaller than that on total LOS. For ED LOS, coefficients were as follows: male sex, 0.85; CCI, 0.151; severe hyponatremia, 11.3; moderate hyponatremia, 2.6; mild hyponatremia, 1.1; mild hypernatremia, 3.7; and moderate/severe hypernatremia, 6.6.

Table 5 shows the rates of hospital admission, ICU admission, death, and LOS for patients with varying degrees of hyponatremia, hypernatremia, and normal Na levels. As expected, the presence of hyponatremia and hypernatremia led to increased rates of hospital admission, which were proportional to the severity of the dysnatremia. Ninety-three percent of patients with severe hyponatremia and 100% of patients with severe hypernatremia were admitted compared to 39% of patients with normal Na levels. This trend was also reflected in ICU admission rates, with severe, moderate, and mild hyponatremia ICU admission rates of 49%, 26%, and 24% recorded, respectively, compared to the lower rate of ICU admission of patients with normal Na levels (23%). For patients with severe, moderate, and mild hypernatremia, the ICU admission rates were 29%, 26%, and 21%, respectively. Rates of death were higher in patients with dysnatremia compared to normal Na levels. For patients with severe, moderate, and mild hyponatremia, death rates were 8%, 5%, and 3%, respectively, while, for those with severe, moderate, and mild hypernatremia, death rates were 57%, 14%, and 5%, respectively. Only 1% of deaths occurred in patients with normal Na levels. Lastly, the LOS data in Table 4 show that abnormal Na levels contributed to increased total and ED LOS times. For all categories (total LOS [all patients], ED LOS, and total LOS [admitted patients]), patients with mild, moderate, and severe hyponatremia and hypernatremia had more LOS hours than those with normal Na levels.

**Table 5.** Disposition and LOS (n=57,427)

Rate	Hyponatremia			Normal	Hypernatremia		
	Mild	Moderate	Severe		Mild	Moderate	Severe
Admitted	2,772 (63)	837 (81)	67 (93)	20,148 (39)	323 (54)	95 (85)	7 (100)
Intensive care unit							
All patients	668 (15)	215 (21)	33 (46)	4,662 (9)	69 (11)	25(22)	2 (29)
Admitted patients only	668 (24)	215 (26)	33 (49)	4,662 (23)	69 (21)	25 (26)	2 (29)
Died	138 (3)	56 (5)	6 (8)	511 (1)	29 (5)	16 (14)	4 (57)
Total LOS (hr)							
All patients <sup>a)</sup>	115 (287)	169 (257)	243 (272)	62 (195)	128 (679)	198 (261)	154 (92)
Admitted patients <sup>a)</sup>	179 (349)	204 (273)	254 (274)	145 (294)	233 (929)	226 (271)	154 (159)
ED LOS (hr)	11 (11)	13 (12)	21 (23)	9 (9)	13 (11)	16 (17)	No cases

Values are presented as number (%).

LOS, length of stay; ED, emergency department.

<sup>a)</sup>Excludes deaths (since it censors LOS).

## DISCUSSION

Sodium disorders are common—one population-based cross-sectional study of > 14,000 adults recorded a hyponatremia prevalence rate of 1.72% in the general population and determined that hyponatremia predicted mortality independent of comorbidities, age, or sex [22]. Multiple studies show that severe hyponatremia and hypernatremia in hospitalized patients is associated with increased morbidity and mortality rates [3–9]. Despite the prevalence and clinical importance of dysnatremia, there is a paucity of literature pertaining to hyponatremia and hypernatremia in the ED. One retrospective study from 2012 evaluated the prevalence and symptoms of hyponatremia and hypernatremia in the ED as well as the correction rates once hospitalized [23] and recorded prevalence rates of 10% and 2% for hyponatremia and hypernatremia in the ED, respectively. Severe hyponatremia (Na < 121 mmol/L) was present in 0.38% of patients who had their Na levels checked, while severe hypernatremia (Na > 149 mmol/L) was present in 0.17%. However, this study was conducted at a single hospital in Switzerland, and its results may not be generalizable to the US population.

Our study found that hyponatremia was more common than hypernatremia in ED patients and determined that mild dysnatremia was more common than severe dysnatremia. Mild, moderate, and severe hyponatremia occurred in 8%, 2%, and 0.1% of patients, respectively, whereas mild, moderate, and severe hypernatremia occurred in 1%, 0.2%, and <0.1% of patients. When assessing mild and moderate hyponatremia cases, the rates were nearly equal in men and women. In contrast, severe hyponatremia was more common in women (64% vs. 36% in men), which is consistent with findings observed in prior studies [5,22,24]. Although not entirely clear, the reasons for this differ-

ence are likely multifactorial and may include sex-related differences in Na metabolism due to estrogen stimulation of arginine vasopressin and increased expression of renal vasopressin receptors leading to greater sensitivity to antidiuretic hormone in women [24–26].

Literature pertaining to sex differences in ED patients with hypernatremia is lacking. More data exist for hospital-acquired hypernatremia, but they are controversial, with some studies showing a female sex predominance [20,27,28] and other studies showing a male sex predominance [23,29]. In our study, there was a slight male sex predominance for mild and moderate hypernatremia, while women were predominant in the severe hypernatremia group (57% female vs. 43% male). However, severe hypernatremia was relatively rare, so an absolute difference of one patient (four women vs. three men) accounted for that observed difference. Nonetheless, we found proportionally more female patients in the extreme ranges of Na derangement (i.e., severe hyponatremia and severe hypernatremia). As expected, the CCI score was greater in all groups of hyponatremia and hypernatremia compared to patients with normal Na levels.

Our study found that patients with dysnatremia were older than those with normal Na levels. The difference was most pronounced in the severe hypernatremia category, with a mean age of 82 ± 15 years compared to mean age of 53 ± 21 years among those with normal Na levels. Our data are consistent with what is already known in the literature, as hypernatremia is more common in patients with impaired thirst or poor access to water, putting elderly patients at particularly high risk. On the other end of the spectrum, hyponatremia is also more common in elderly patients due to increased comorbidities (renal insufficiency, heart failure, etc.), diuretic use, and the syndrome of inappropriate antidiuretic hormone [7].

Our outcomes data demonstrate that both hyponatremia and hypernatremia in the ED are associated with increased risks of hospitalization, ICU admission, and death. The increases in adverse outcomes are proportional to the severity of Na derangement. Due to the retrospective and observational nature of this study, it is unclear whether the abnormality in Na concentration itself is the cause of the increased morbidity and mortality rates. Dysnatremia may also be a marker of disease severity, where the associated morbidity and mortality result from the underlying disease leading to the abnormal Na level. In some patients, both a deranged Na level and underlying diseases may have contributed to worse outcomes. These findings are not surprising, as prior studies have also shown that Na derangements are associated with higher rates of hospitalization and morbidity/mortality [3–9]. A study by Arampatzis et al. [23] found that > 20% of ED patients with severe hyponatremia ( $\text{Na} < 121 \text{ mmol/L}$ ) and hypernatremia ( $\text{Na} > 149 \text{ mmol/L}$ ) required ICU admission and that morbidity was greater in patients with severe hypernatremia (28%) than those with severe hyponatremia (13%). Surprisingly, 46% of patients with severe hypernatremia had no Na level checked the next day, and 18% received no treatment for their hypernatremia. These rates were higher than those of patients with severe hyponatremia (among whom 14% had no Na level checked the next day and only 4% received no treatment). Although this study was performed at a hospital in Switzerland, it highlights the importance of recognizing and properly treating severe dysnatremia. Similarly, our study found that, although hyponatremia was more common, patients with hypernatremia had worse outcomes. While the aORs of mortality were higher for all categories of hypernatremia compared to hyponatremia, the difference was most pronounced in the severe category. Compared to those for a normal Na level, the aOR (95% CI) values of mortality for severe hypernatremia were 55.75 (11.37–273.30) compared to 6.98 (2.87–16.40) for severe hyponatremia. We also found that age (OR, 1.048; 95% CI, 1.043–1.053) and female sex (OR, 0.70; 95% CI, 0.60–0.81) were associated with mortality.

Our LOS data revealed that, for all severities of hyponatremia and hypernatremia, the LOS was increased compared to that of patients with normal Na levels. In general, the severity of Na derangement was proportional to the increase in LOS time, with more severe Na derangements leading to even longer LOS times. An exception to this can be seen in the total LOS (admits only) in Table 3, where the coefficient for mild hypernatremia was 84.2 compared to that of 70.7 for moderate/severe hypernatremia. The reason for this is unclear, as deaths were excluded. Regardless, it remains clear that both hyponatremia and hypernatremia, when present, lead to an increased LOS.

Our study has several important limitations. A major limitation of our study is its retrospective nature, which is subject to numerous biases. Thus, our results demonstrate associations and cannot establish causality. As such, the results should be considered exploratory or hypothesis-generating only. As a single-center study at a large suburban academic hospital, our results may not be generalizable to different patient populations and other clinical settings. Additionally, as a retrospective chart review, our results are susceptible to selection bias. Although not a unique limitation to our study, different studies use different cutoffs to define mild, moderate, and severe dysnatremia. As such, the definitions we used may differ from those of other studies, which could impact how the data are interpreted. We did not evaluate the causes or chronicity of hyponatremia or hypernatremia in our study cohort. As these factors may significantly impact patient outcomes, future studies could yield more robust information by collecting these data. It is impossible to know the degree to which the mortality observed in our study was attributable to the dysnatremia versus other comorbid conditions, so our results are subject to residual confounding.

Hyponatremia and hypernatremia are commonly discovered in the ED, and both were associated with higher rates of hospital admission, ICU admission, and mortality. They are also associated with prolonged hospital LOS times. The study outcomes worsened according to the severity of Na derangement.

## ETHICS STATEMENTS

As a retrospective chart review, the requirement for informed consent was waived.

## CONFLICT OF INTEREST

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

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None.

## AUTHOR CONTRIBUTIONS

Conceptualization: all authors; Data curation: AJS, HCT, WFP; Formal analysis: all authors; Methodology: AJS, HCT; Visualization: all authors; Writing—original draft: KO, AJS, HCT; Writing—review & editing: all authors. All authors read and approved the final manuscript.

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# Usability testing of a blind intubation device for intubation novices: a randomized crossover simulation study

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**Objective** A new blind intubation device (BID) has been developed for endotracheal intubation. This study aimed to test the usability of the BID in comparison to direct laryngoscopy (DL) and video laryngoscopy (VL) with inexperienced healthcare providers for endotracheal intubation.

**Methods** This was a randomized crossover simulation study. Participants who had conducted fewer than five live intubation sessions were included in the study. The manikin simulation was conducted using a Laerdal trainer airway manikin. Participants performed intubation using all three devices, DL, VL, and BID. The primary outcome was intubation success rate in the first pass the secondary outcome was intubation time to first ventilation, and the tertiary outcome was dental injury.

**Results** A total of 45 healthcare workers who were novices in intubation participated in this study, including 13 physicians (interns), 14 emergency medical technicians, and 18 nurses. The intubation success rates in the first pass with BID, DL, and VL were 93.3%, 91.1%, and 97.8%, respectively ( $P=0.53$ ). The intubation times to first ventilation with BID, DL, and VL were  $13.15 \pm 6.16$ ,  $19.07 \pm 7.71$ , and  $17.31 \pm 6.57$  seconds, respectively ( $P < 0.01$ ). The proportions of dental injuries associated with BID, DL, and VL were 0% for physicians; 28.6%, 14.3%, and 0%, respectively for emergency medical technicians; and 27.8%, 11.1%, and 16.7%, respectively for nurses.

**Conclusion** We performed a pilot study to test the usability of the new BID. There was no significant difference in intubation success rate in the first pass among BID, DL, and VL. The intubation time to first ventilation was shorter with the BID compared to DL and VL.

**Keywords** Airway management; Intratracheal intubation; Equipment and supplies; Pilot projects

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## Capsule Summary

### What is already known

*Endotracheal intubation is life-saving procedure for securing the airway. The development of prehospital treatment has also led to the implementation of endotracheal intubation in out-of-hospital settings. However, it is difficult for pre-hospital healthcare providers to get enough opportunities to undertake live endotracheal intubation, and the use of alternative supraglottic airway devices like the laryngeal mask airway, Combitube, and i-gel has increased. However, considering the human airway anatomy, endotracheal intubation is still the gold standard for managing secretions, and securing and facilitating optimal oxygenation and ventilation when conducted correctly.*

### What is new in the current study

*We developed a simple intubation device. The new intubation device is called the "blind intubation device (BID)," and it was designed for blind intubation through the patient's vocal cord to facilitate endotracheal intubation instead of a supraglottic airway. The first pass success rate with the BID was similar to direct laryngoscopy and video laryngoscopy, and the time to ventilation was shortest with the BID.*

## INTRODUCTION

Endotracheal intubation (ETI) is life-saving procedure for securing the airway [1]. Critically ill patients require ETI in various situations such as operating rooms (ORs), in-hospital general wards, intensive care units (ICUs), and emergency departments (EDs) [2]. Advancements in prehospital treatment have led to the implementation of ETI in out-of-hospital settings [3].

Prior research has reported that experience, knowledge, and skill of prehospital healthcare providers are important for successful intubation [4]. To maintain certain success rates, more than 30 live ETI sessions are required for professionals to be skilled in the procedure [5]. However, it is difficult for prehospital healthcare providers to gain experience with live ETI, and the use of alternative supraglottic airway (SGA) devices like the laryngeal mask airway, Combitube (Tyco Healthcare Nellcor), and i-gel (Intersurgical) has increased [6]. The benefit of using SGAs instead of ETI has been questioned, and there are no definite guidelines for airway device selection in prehospital settings [7–9]. However, considering the human airway anatomy, ETI remains the gold standard for managing secretions and securing and facilitating optimal oxygenation and ventilation when conducted correctly [10].

Video laryngoscopy (VL), which is indirectly used to visualize the glottis and vocal cords, is a relatively recent and advanced intubation technology that has been widely used in the ICU and OR [11]. However, the success rate of VL is dependent on operator competency and the intubation environment, and its expense is high. Guyette et al. [12] reported that the use of VL by prehospital transport agencies did not reduce the number of intubation attempts or success rate associated with direct laryngoscopy (DL) performed by highly trained medical personnel. In another study,

Nouruzi-Sedeh et al. [13] reported that VL success rate was greater than 90% compared with 51% for DL in the elective intubation of patients in the OR administered by untrained medical personnel. In hospital general ward settings, VL is reported to have a higher first-attempt success rate than DL, but the results were not significant in ICU or prehospital settings [11,12,14,15]. Even though VL has demonstrated better performance, it has a high cost, which has limited its widespread use, especially for prehospital ambulance services with a limited budget [15].

Because of the difficulty in learning and performing intubation and the high cost of VL for prehospital healthcare providers who are likely to encounter emergent airway cases, we developed a simple intubation device. The new blind intubation device (BID) was designed for blind intubation without the need to visualize the vocal cords. The purpose of this study was to test the usability of the newly developed BID compared with traditional DL and VL.

## METHODS

### Ethics statements

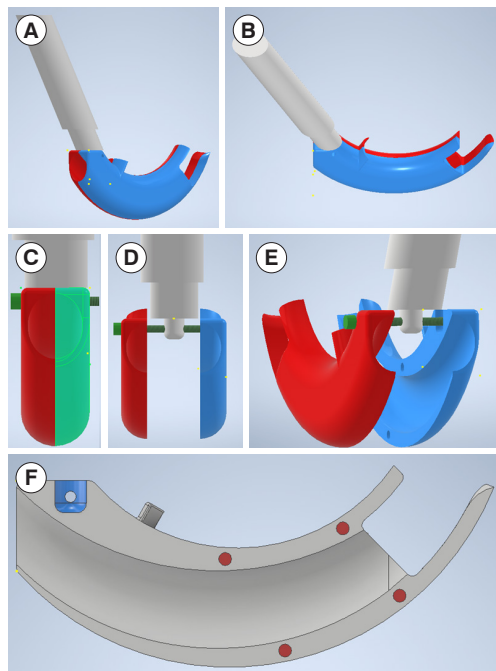
The study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (No. B-2007/622-305). The participants provided written informed consent for the study using the Seoul National Bundang Hospital research consent form.

### Design and function of the blind intubation device

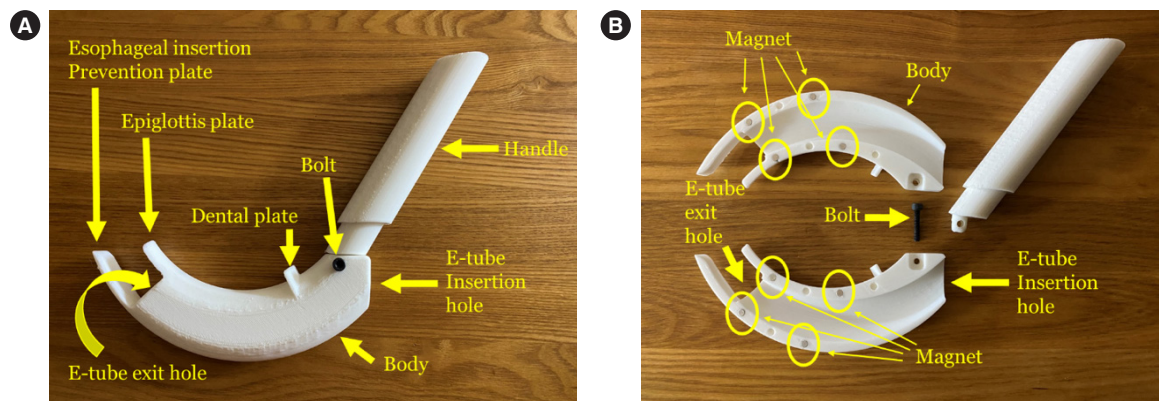
The BID (Fig. 1) was designed using the three-dimensional (3D) design program, Inventor 2020 (Autodesk). The BID consists of a handle and a body that are connected via a bolt at the end of the handle tip. There is an endotracheal tube (E-tube) insertion hole allowing the E-tube to pass through an epiglottis plate located

above the glottis, an esophageal plate that prevents esophageal insertion, and an E-tube exit hole located in front of the vocal cords if placed correctly. Each body part has magnets to attach them into one device. The dental plate indicates the body insertion depth. Insertion of the BID body should stop when the dental plate touches the patient's lower incisors. The design was printed using a 3D printer (Cubicon) and is constructed of polylactic acid (Fig. 2).

For ETI, the BID must be placed in the manikin airway (Fig. 3A). When the dental plate touches the lower incisor of the patient, the handle needs to be pulled back to avoid injuring the teeth



**Fig. 1.** The design of the blind intubation device using Inventor 2020 (Autodesk). (A) Lateral view. (B) Superior view. (C) Posterior view. (D) Separated form. (E) Lateral view of separated form. (F) Cross-sectional view.



**Fig. 2.** The components of the blind intubation device. The name of components viewed (A) from the side and (B) from the separated form. E-tube, endotracheal tube.

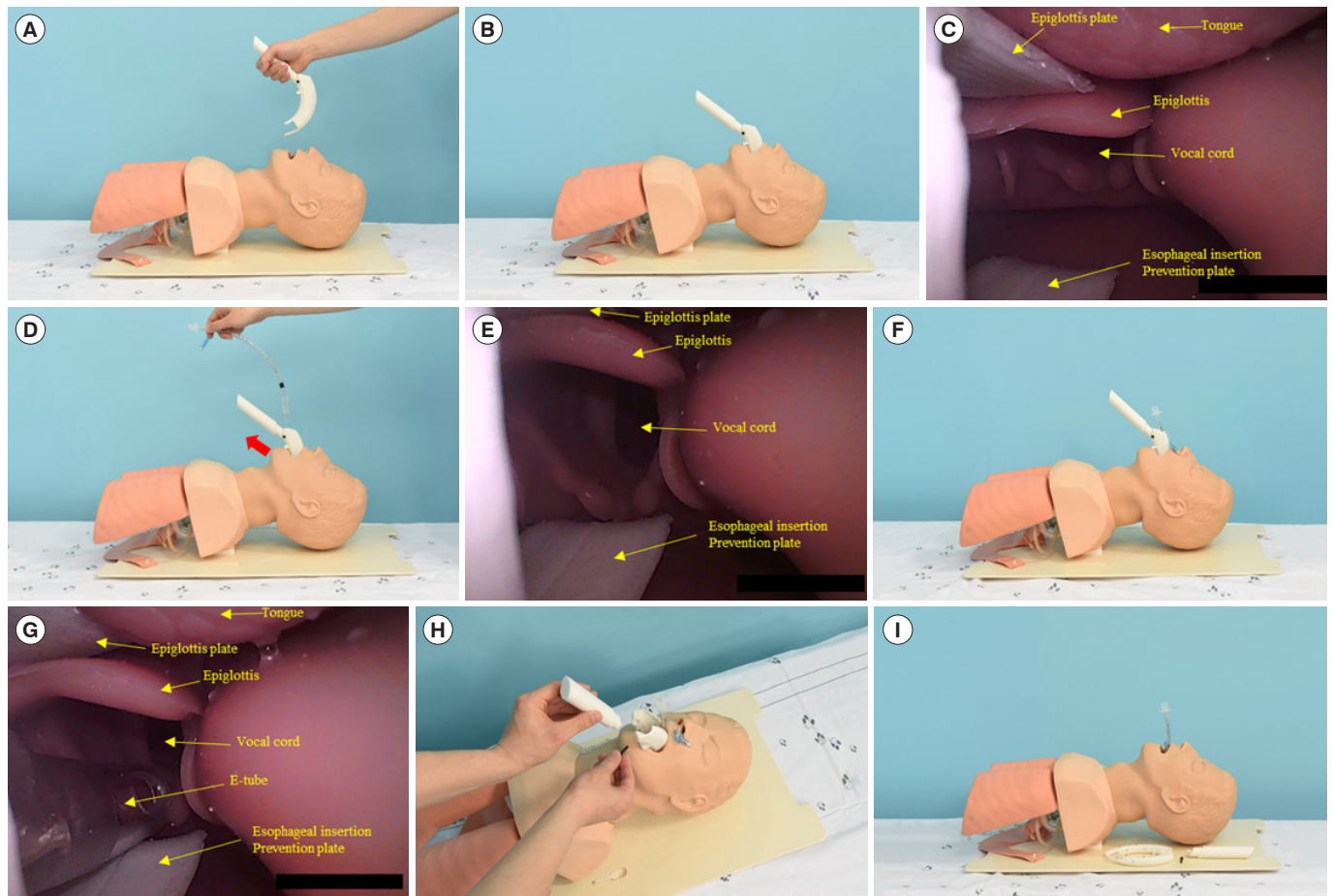
(Fig. 3B). Intraoral status when the BID is placed correctly is illustrated in Fig. 3C. To insert the E-tube, the handle needs to be pushed along the direction of the red arrow to elevate the epiglottis and expose the vocal cords (Fig. 3D). The intraoral status when the handle is elevated along the direction of the red arrow is described in Fig. 3E. Compared to image in Fig. 3C, the epiglottis is elevated, the vocal cords are exposed, and the esophageal insertion prevention plate blocks the esophageal entrance (Fig. 3E). The E-tube is inserted into the BID E-tube insertion hole. The E-tube exit hole is located in front of the vocal cords, and advancement of the E-tube naturally results in ETI (Fig. 3F, G). After successful intubation is confirmed by end-tidal carbon dioxide (EtCO<sub>2</sub>) monitoring or lung auscultation, the handle and the body of the BID can be disassembled (Fig. 3H). The E-tube remains in the trachea after removal of the BID from the patient's mouth (Fig. 3I).

### Study design

This randomized crossover simulation study used manikins to evaluate DL, VL, and BID performance. It was conducted between September and October 2020 at a tertiary teaching hospital with an annual ED volume of approximately 80,000 patients and 600 ETI cases in Gyeonggi Province, Korea.

### Participants

The expected sample size was at least 12 participants for each group based on a previous study [16]. We finally determined a size of 40 participants based on a dropout rate of 10%. The participants were recruited from the ED using an intrahospital announcement bulletin board, and all provided written informed consent for the study. The participants included physicians, nurses, and emergency medical technicians (EMTs) aged between 18 and 60 years who had performed fewer than five live intubations.



**Fig. 3.** The way to perform endotracheal intubation using the blind intubation device (BID). (A) Initial placement of the BID. (B) Proper placement of the BID. (C) Intraoral status when the BID is properly placed. (D) Elevation of the epiglottis before inserting the endotracheal tube (E-tube). (E) Intraoral status when the epiglottis is elevated. (F) Proper placement of the E-tube through the BID. (G) Intraoral status when the E-tube passes the BID. (H) Removal of the BID after successful endotracheal intubation. (I) Lateral view after successful endotracheal intubation.

Participants were excluded if they did not consent to the study; had cardiac, neurological, or musculoskeletal disease; or were pregnant.

### Study protocol

The researcher lectured all participants on DL, VL, and BID for approximately 30 minutes before simulation. The participants had 30 minutes of practice on a manikin with each device for familiarization with the ETI procedure. During the actual test, the participants were allowed two attempts using the manikin for each device. Macintosh DL was used with a fiber optic curved Mac 4 blade (Heine Optotechnik). The Glidescope GVL (Verathon Medical) was used for VL. A GlideRite stylet (Verathon Medical) was used for both DL and VL intubations. A cuffed polyvinyl chloride E-tube with an internal diameter of 7.5 mm was used for all intubation sessions. A Laerdal airway management trainer (Laerdal) was used as the intubation manikin, which was maintained in the

supine position, and the sniffing position was allowed if the operator could not find the vocal cords.

The participants were randomly allocated to six groups based on the order of the intubation technique (Fig. 1): group 1 (DL-VL-BL), group 2 (DL-BL-VL), group 3 (VL-DL-BL), group 4 (VL-BL-DL), group 5 (BL-DL-VL), and group 6 (BL-VL-DL). Randomization was achieved by drawing lots using eight identical papers for each of the six groups.

After allocation, the participants conducted ETI using each device in sequential order. A single unblinded researcher (DKK) used a stopwatch to record the intubation time. The participants were blinded to the measurements. Intubation was defined as successful when the lungs of the manikin inflated well. Intubation was considered a failure if it took more than 60 seconds or esophageal intubation was confirmed. For the participants who failed during the first attempt, a second attempt was allowed. The participants had a 1-minute break after each intubation procedure.

A dental injury was recorded if a click sound was generated from the upper incisors of the manikin. All intubation processes were performed in a normal stretcher car with a height of 90 cm.

All participants completed a brief questionnaire that was used to collect the following data: demographic data (age, sex, profession, working experience as healthcare provider), Cormack Lehane grade of the manikin, difficulty with ETI manipulation, and general satisfaction with each device [17]. The difficulty (range, 1 [very easy] to 5 [very difficult]) and general satisfaction (range, 1 [excellent] to 5 [very poor]) associated with each device were expressed on a 5-point Likert scale.

### Exposure and outcome variables

The primary outcome was the success rate of intubation during the first attempt. The secondary outcome was intubation time to first ventilation in the first attempt. Intubation time to first ventilation was defined as the duration from the time the laryngoscopy blade of the DL or VL or the body of the BID passed the incisors of the manikin to the first ventilation with a bag-valve mask. The third outcome was dental injury rate.

### Statistical analysis

Categorical variables are presented as counts and proportions and were compared using Fisher exact test. Continuous variables

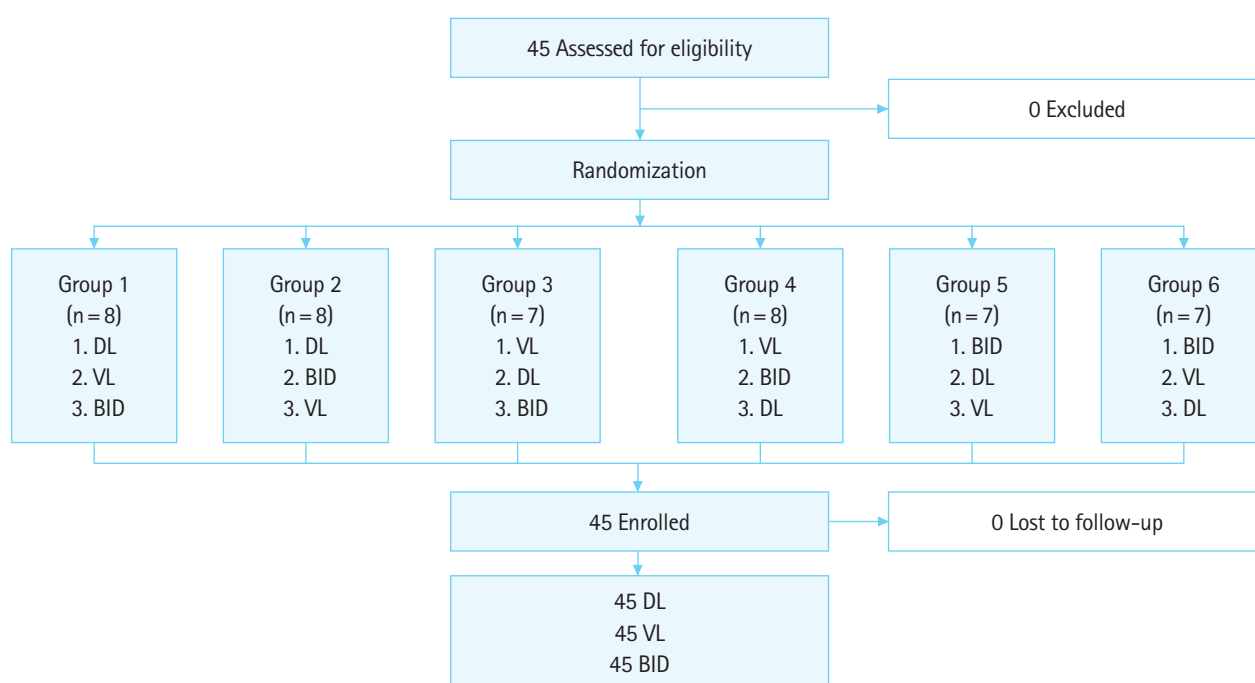


Fig. 4. Study flowchart. DL, direct laryngoscopy; VL, video laryngoscopy; BID, blind intubation device.

Table 1. Demographic findings for each profession

Demographic finding	Profession				P-value
	All	Physician	EMT	Nurse	
No. of participants	45 (100)	13 (28.9)	14 (31.1)	18 (40.0)	NA
Age (yr)	27 (25–29)	25 (24–29)	27 (25–28)	28 (27–30)	< 0.01
Female sex	35 (77.8)	8 (61.5)	10 (71.4)	17 (94.4)	< 0.01
Working experience (mo)	36 (7–60)	7 (6–7)	38 (27–54)	58 (39–90)	< 0.01
Prior intubation experience					
Direct laryngoscopy	0 (0–1)	2 (1–2)	0 (0–1)	0 (0–0)	NA
Video laryngoscopy	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	NA
Supraglottic airway	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	NA

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

EMT, emergency medical technician; NA, not applicable.

are presented as the median and interquartile range (IQR) or mean  $\pm$  standard deviation and were compared using the analysis of variance test. All analyses were performed using SAS ver. 9.4 (SAS Institute Inc). Statistical significance was set at  $P < 0.05$ .

## RESULTS

A total of 45 participants was recruited for the study. No participants were excluded. Participants were allocated to six groups, and a total of 135 intubations were performed, with 45 cases for each intubation device (Fig. 4).

The median age of the participants was 27 years (IQR, 25–29 years). The number of female participants was 35 (77.8%). The numbers of physicians, EMTs, and nurses were 13 (28.9%), 14 (31.1%), and 18 (40.0%), respectively. The median working expe-

**Table 2.** Intubation performance for each intubation device

Variable	BID (n = 45)	DL (n = 45)	VL (n = 45)	P-value
Cormack Lehane grade	NA	1.53 $\pm$ 0.63	NA	NA
Difficulty of device <sup>a)</sup>	1.58 $\pm$ 0.66	3.22 $\pm$ 0.85	2.16 $\pm$ 0.95	< 0.01
Satisfaction with device <sup>b)</sup>	1.40 $\pm$ 0.65	2.82 $\pm$ 0.91	1.87 $\pm$ 0.76	< 0.01
First pass success	42 (93.3)	41 (91.1)	44 (97.8)	0.53
First pass intubation time to first ventilation (sec)	13.15 $\pm$ 6.16	19.07 $\pm$ 7.71	17.31 $\pm$ 6.57	< 0.01
Second pass success	3 (100)	4 (100)	1 (100)	NA
Dental injury	9 (20.0)	4 (8.9)	3 (6.7)	0.17
Cause of failure				0.07
More than 60 sec	2 (4.4)	0 (0)	1 (2.2)	
Esophageal intubation	1 (2.2)	4 (8.9)	0 (0)	

Values are presented as mean  $\pm$  standard deviation or number (%).

BID, blind intubation device; DL, direct laryngoscopy; VL, video laryngoscopy; NA, not applicable.

<sup>a)</sup>Range, 1 (very easy) to 5 (very difficult). <sup>b)</sup>Range, 1 (excellent) to 5 (very poor).

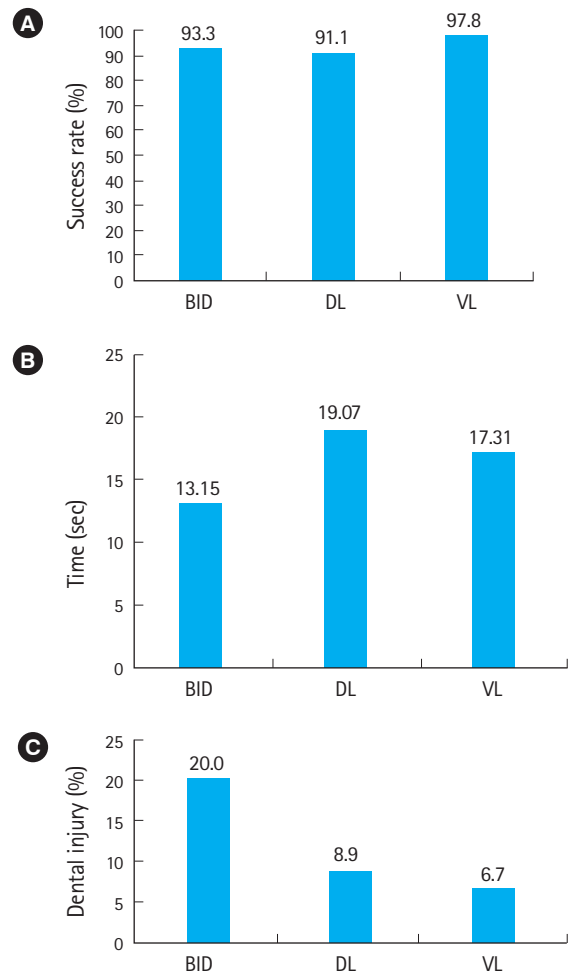
**Table 3.** Subgroup analysis of outcomes by profession

Variable	Physician (n = 13)			EMT (n = 14)			Nurse (n = 18)		
	BID	DL	VL	BID	DL	VL	BID	DL	VL
Cormack Lehane grade	NA	1.46 $\pm$ 0.52	NA	NA	1.43 $\pm$ 0.51	NA	NA	1.67 $\pm$ 0.77	NA
Difficulty of device <sup>a)</sup>	1.77 $\pm$ 0.60	3.00 $\pm$ 0.71	2.23 $\pm$ 1.01	1.57 $\pm$ 0.76	3.00 $\pm$ 0.68	2.14 $\pm$ 0.86	1.44 $\pm$ 0.62	3.56 $\pm$ 0.98	2.11 $\pm$ 1.02
Satisfaction with device <sup>b)</sup>	1.38 $\pm$ 0.51	2.77 $\pm$ 0.83	1.92 $\pm$ 0.64	1.57 $\pm$ 0.94	2.57 $\pm$ 0.85	2.00 $\pm$ 0.96	1.28 $\pm$ 0.46	3.06 $\pm$ 1.00	1.72 $\pm$ 0.67
First pass success	13 (100)	13 (100)	13 (100)	11 (78.6)	13 (92.9)	14 (100)	18 (100)	15 (83.3)	17 (94.4)
First pass intubation time to first ventilation (sec)	10.98 $\pm$ 4.06	17.47 $\pm$ 5.02	16.40 $\pm$ 5.66	12.44 $\pm$ 4.14	19.70 $\pm$ 11.63	15.49 $\pm$ 5.62	15.28 $\pm$ 8.04	19.74 $\pm$ 5.45	19.39 $\pm$ 7.55
Second pass success (%)	NA	NA	NA	3 (100)	1 (100)	NA	NA	3 (100)	1 (100)
Dental injury	0 (0)	0 (0)	0 (0)	4 (28.6)	2 (14.3)	0 (0)	5 (27.8)	2 (11.1)	3 (16.7)
Cause of failure									
More than 60 sec	0 (0)	0 (0)	0 (0)	2 (14.3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5.6)
Esophageal intubation	0 (0)	0 (0)	0 (0)	1 (7.1)	1 (7.1)	0 (0)	0 (0)	3 (16.7)	0 (0)

Values are presented as mean  $\pm$  standard deviation or number (%).

EMT, emergency medical technician; BID, blind intubation device; DL, direct laryngoscopy; VL, video laryngoscopy; NA, not applicable.

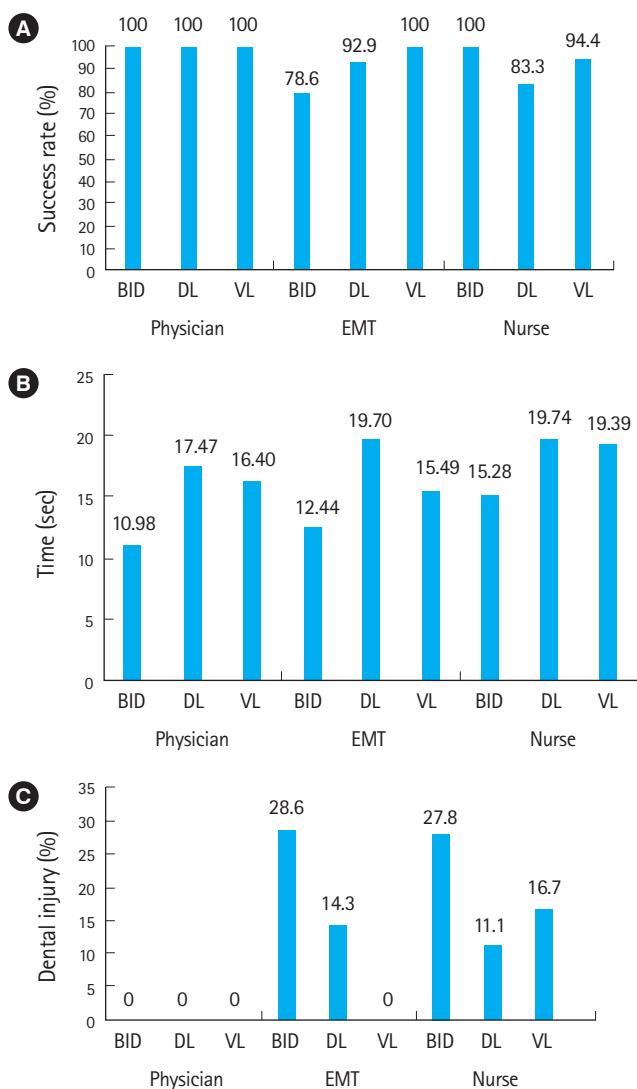
<sup>a)</sup>Range, 1 (very easy) to 5 (very difficult). <sup>b)</sup>Range, 1 (excellent) to 5 (very poor).



**Fig. 5.** Comparison of outcomes of the intubation devices. Values on the bar represent means. (A) First pass intubation success rate. (B) Intubation time to first ventilation in first attempt. (C) Dental injury. BID, blind intubation device; DL, direct laryngoscopy; VL, video laryngoscopy.

rience for the healthcare providers was 36 months (IQR, 7–60 months). The median number of previous intubation experiences was zero for DL, VL, and SGA, but the IQR was 0 to 1 for the DL group (Table 1).

The mean Cormack Lehane grade of the intubation manikin rated by participants was  $1.53 \pm 0.63$ . Intubation success rate for the first attempt in the BID, DL, and VL groups was 93.3%, 91.1%, and 97.8%, respectively ( $P=0.53$ ). The mean intubation time to first ventilation in the first attempt was  $13.15 \pm 6.16$ ,  $19.07 \pm 7.71$ , and  $17.31 \pm 6.57$  seconds for the BID, DL, and VL groups, respectively ( $P<0.01$ ). The proportions of dental injuries in BID, DL, and VL were 20.0%, 8.9%, and 6.7%, respectively ( $P=0.17$ ) (Table 2



**Fig. 6.** Subgroup comparison of the outcomes by profession: 13 physicians, 14 emergency medical technicians (EMTs), and 18 nurses. Values on the bar represent means. (A) First pass intubation success rate. (B) Intubation time to first ventilation in first trial. (C) Dental injury. BID, blind intubation device; DL, direct laryngoscopy; VL, video laryngoscopy.

and Fig. 5). For participants who failed in the first attempt, the intubation success rate for the second attempt was 100% for all groups. The number of intubation failures due to need for more than 60 seconds was two (4.4%) for BID, zero for DL, and one (2.2%) for VL. The number of esophageal intubations was one (2.2%) for BID, four (8.9%) for DL, and zero for VL. The mean difficulty associated with using each intubation device expressed on a 5-point Likert scale was  $1.58 \pm 0.66$  for BID,  $3.22 \pm 0.85$  for DL, and  $2.16 \pm 0.95$  for VL. The mean satisfaction for each intubation device expressed on a 5-point Likert scale was  $1.40 \pm 0.65$  for BID,  $2.82 \pm 0.91$  for DL, and  $1.87 \pm 0.76$  for VL (Table 2).

Table 3 shows the subgroup comparisons by profession. The intubation success rates for BID, DL, and VL were all 100% for physicians; 78.6%, 92.9%, and 100%, respectively, for EMTs; and 100%, 83.3%, and 94.4%, respectively, for nurses. The mean intubation time to first ventilation in the first attempt for BID, DL, and VL was  $10.98 \pm 4.06$ ,  $17.47 \pm 5.02$ , and  $16.40 \pm 5.66$  seconds, respectively, for physicians;  $12.44 \pm 4.14$ ,  $19.70 \pm 11.63$ , and  $15.49 \pm 5.62$  seconds, respectively, for EMTs; and  $15.28 \pm 8.04$ ,  $19.74 \pm 5.45$ , and  $19.39 \pm 7.55$  seconds, respectively, for nurses (Table 3). The proportions of dental injuries associated with BID, DL, and VL were all 0% for physicians; 28.6%, 14.3%, and 0%, respectively, for EMTs; and 27.8%, 11.1%, and 16.7%, respectively, for nurses (Table 3 and Fig. 6).

## DISCUSSION

A new intubation device was developed, and its usability was tested in this pilot study. The BID showed no significant difference in intubation success rate in the first attempt compared to DL or VL. The intubation time to first ventilation was shorter in the BID compared to DL or VL.

In existing SGAs, though the insertion process is easy, misplacement or esophageal insertion is frequent, resulting in inefficient ventilation. The BID mechanically prevented esophageal insertion by attaching an esophageal insertion prevention plate to the end of the body. Furthermore, for convenience of inexperienced operators, the insertion depth was marked with a dental plate to ensure an appropriate insertion depth and location inside the mouth. The epiglottic plate is designed to be placed under the glottis to elevate the epiglottis as in DL. The BID was designed to preoccupy the intraoral space where the E-tube is supposed to be inserted successfully, such that the operator can advance the E-tube according to the preoccupied intraoral space through the BID, resulting in endotracheal placement. In addition, the BID is disposable, reducing infection, and is operable without a battery.

The performance varied by intubation device. The intubation

success rate was highest for VL and lowest for DL, although the difference was not statistically significant. Previous studies have reported different intubation outcomes stratified by profession and previous experience with airway management [12,13,18–20]. Although there was no statistical analysis for profession comparison, physicians showed the highest intubation success rate regardless of device. This result is consistent with those of previous studies showing that physicians had higher intubation success rates than nonphysicians [20]. Inexperienced doctors showed the highest success rate with the least working experience compared with other professions. In addition, physicians had more previous intubation experience than other professions. This may have been caused by differences in the education systems for the various professions. In contrast, nurses had the longest working experience with no previous intubation experience. The BID showed the lowest success rate in the EMT group and the highest success rate in the nurse group. The difference in BID outcomes stratified by profession implies that further research is required to determine the effect of previous education on the use of the device.

VL is a well-known intubation device with advanced technology [14]. However, considering the high cost of VL products, they can only be used in certain hospital settings, such as the OR, ICU, and ED, which limits their usefulness outside the hospital. The cost of VL and DL varies according to country and manufacturer, ranging from €1,120 to €5,600 for VL and \$100 to \$300 for DL, while the BID costs less than \$100 [21]. For BID, the intubation time to first ventilation was shortest because it does not require a stylet for E-tube insertion. Although there was no statistical difference in dental injury, the BID showed the highest rate because the airway manikin did not have enough intraoral space due to the absent mandibular joint function. Further usability testing on an airway manikin with a mandible joint and prior education on BID handling are required to reduce the dental injury rate.

The difficulty and satisfaction associated with usage were highest for BID, because the BID could be used in the blind state and allowed faster intubation than DL and VL. For the failed cases of the DL and VL, the operators did not locate the vocal cords because the blade was inserted too deeply. One case of esophageal intubation was observed in the BID group. During the practice trial before the actual test, some participants could not find the vocal cords using the VL. Similar cases were observed with DL in practice trials. Despite the BID design to prevent esophageal intubation when performed correctly, esophageal intubation with the BID was problematic. Likewise for DL, the BID needs to be elevated against gravity to expose the vocal cords. Esophageal intubation with the BID may have occurred because of insufficient

elevation of the glottis and inappropriate positioning of the device inside the mouth. Education on correct usage of the BID is required before use in further studies.

We included physicians, EMTs, and nurses as inexperienced participants because they are most likely to encounter patients with airway compromise in the clinical arena, and the purpose of the BID is to assist ETI by inexperienced operators. We included nurses in the study because in some emergency medical service systems, nurses participate as prehospital emergency medical service providers [22,23]. We found that short lectures and practice on airway manikins facilitated ETI with BID without previous intubation experience. The BID can be useful when VL cannot be performed due to expense and in prehospital ambulance or in-hospital ward situations. Although the satisfaction, difficulty, and outcomes associated with BID were better than those associated with DL in this pilot study, the outcomes should be confirmed by further studies using a more exact sample size calculation. In further research, the BID needs to be compared with the SGAs because they have similar esophageal insertion prevention functions and are widely used in the prehospital setting.

This study has several limitations. First, it was a pilot simulation study. Because this device is new, there is no reference information for comparison of its function. Based on the results of this study, we can design appropriate studies for analysis and protocols for comparing BID feasibility with other airway devices. Second, this study was performed on an airway manikin, not on real human patients. Because of ethical problems trying new medical devices directly on humans, further studies on this new device are required for various airway manikins. Third, there were measurement errors in determining intubation duration during simulation due to measurement by a single unblinded researcher. Fourth, this study was repeated by the same operator, and the procedure performed immediately before could have influenced the procedure performed later. Further research is needed to separate the study population groups. Last, as there are several VL products available on the market, the use of only one may have biased the results.

The BID was developed, and its feasibility was tested on airway manikins. The BID showed a similar first intubation success rate and shorter intubation time to first ventilation compared with DL or VL. Further research with an accurate sample size calculation based on this pilot study is required.

## SUPPLEMENTARY MATERIALS

**Supplementary Material 1.** Questionnaire used for the participants.

Supplementary material is available from <https://doi.org/10.15441/ceem.22.370>.

## ETHICS STATEMENTS

The study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (No. B-2007/622-305). The participants provided written informed consent for the study using the Seoul National Bundang Hospital research consent form.

## CONFLICT OF INTEREST

Dae Kon Kim has applied for a patent for the device described in this study, and the result is pending. No other potential conflict of interest relevant to this article was reported.

## FUNDING

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## AUTHOR CONTRIBUTIONS

Conceptualization: YJK; Data curation: JJ; Formal analysis: DKK; Funding acquisition: JJ; Investigation: DKK, SMP; Methodology: YJK, SMP; Project administration: DKK, JJ; Resources: DKK, JJ; Software: YJK; Supervision: YH Jo; Validation: SMP, YH Joo; Visualization: YH Jo; Writing—original draft: DKK; Writing—review & editing: YJK, JJ, YH Jo, YH Joo, SMP. All authors read and approved the final manuscript.

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# The effect of regional distribution of isolation rooms in emergency departments on ambulance travel time during the COVID-19 pandemic

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**Objective** The number and distribution of isolation rooms in Korea differ by region. The distribution of isolation beds in emergency departments may have affected ambulance travel time and burden on emergency medical service (EMS) during the COVID-19 pandemic.

**Methods** This retrospective observational study analyzed EMS records in four regions of the Gyeonggi Province, Korea, from January 01, 2019 to December 31, 2020. The main exposure was the number of emergency department isolation rooms in each region. The primary outcome was call-to-return time for the EMS. The interaction effect of the number of regional isolation rooms on the call-to-return time during the COVID-19 pandemic was analyzed using a generalized linear model (GLM) and logistic regression.

**Results** A total of 781,246 cases was included in the analyses. During the COVID-19 pandemic, the call-to-scene time (before 8 minutes vs. after 9 minutes,  $P < 0.05$ ) and call-to-return time (before 46 minutes vs. after 52 minutes,  $P < 0.05$ ) for emergency patients increased significantly compared to before the pandemic. As the number of regional isolation rooms increased, the effect of COVID-19 on the call-to-return time decreased significantly in the multivariable GLM with an interaction term (with 10.14 isolation rooms per million population: adjusted exponential  $\beta$  coefficient [ $\exp(\beta)$ ], 1.33; with 12.24 isolation rooms per million population: adjusted  $\exp(\beta)$ , 1.18). As the number of regional isolation rooms increased, the effect of COVID-19 on the call-to-scene time decreased significantly in the multivariable GLM with an interaction term (with 10.14 isolation rooms per million population: adjusted  $\exp(\beta)$ , 1.20; with 12.24 isolation rooms per million population: adjusted  $\exp(\beta)$ , 1.09).

**Conclusion** During the pandemic, the increases in call-to-return time and call-to-scene time were smaller in regions with more isolation rooms per population.

**Keywords** Isolation hospitals; Emergency medical services; COVID-19

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## Capsule Summary

### What is already known

Isolation beds within the region are unevenly distributed by region, and quarantine beds are an essential medical resource for treating suspected COVID-19 patients.

### What is new in the current study

Emergency medical service travel time was longer during the COVID-19 pandemic in regions with fewer isolated beds in emergency rooms.

## INTRODUCTION

COVID-19 is a novel infectious disease caused by the SARS-CoV-2 virus and has spread across the world [1,2]. In Korea, the community spread of COVID-19 was confirmed on February 20, 2020 [3]. The burden on the entire emergency medical system increased during the COVID-19 pandemic [4,5], especially for the prehospital stage, where delays in hospital transport of emergency patients were reported [6–8]. Kim et al. [9] reported that the hospital transport time for patients with suspected acute stroke with neurological deficits was delayed by 4 minutes during the COVID-19 pandemic. Additionally, according to Lim et al. [10], the emergency medical service (EMS) response time for out-of-hospital cardiac arrest patients was significantly delayed, and the survival rates decreased. Therefore, the EMS response and transfer times increased, increasing their burden and affecting patient prognosis during the pandemic.

The EMS is tightly associated with regional emergency medical resources. Isolation rooms of an emergency institution are an essential resource for treating patients with suspected COVID-19 symptoms, including fever and respiratory symptoms [11,12]. In Korea, the minimum number of isolation rooms in an emergency department (ED) is stipulated by law according to the tier of the emergency medical institution. However, as most emergency medical institutions in Korea are private hospitals, there is an imbalance of emergency medical institutions between regions. Consequently, the distribution of isolation rooms differs by region, which may affect the prehospital transport phase of patients and the burden on EMS. This study was conducted to analyze the effect of the imbalance in emergency medical resource distribution between regions on the prehospital stage during the COVID-19 pandemic. For this purpose, the effect of the number of isolation rooms by region on ambulance travel time of EMS during the COVID-19 pandemic was analyzed.

## METHODS

### Ethics statements

This study was approved by the Institutional Review Board of Seoul Medical Center (No. SEOUL 2022-03-013). The need for informed consent was waived due to the retrospective nature of the study.

### Study design

This was a retrospective, observational study of patients who used the 119 service, which is the EMS operated by the Korean government, in four regions of Gyeonggi Province—northeast,

northwest, southeast, and southwest—from January 1, 2019 to December 31, 2020. All ambulance run sheets recorded by the EMS crew were analyzed, and the cases including call time, dispatch time, scene arrival time, and return time were analyzed. The main exposure was the number of isolation rooms in the region. The primary outcome was the change in elapsed time interval from call time to station return time (call-to-return time) before and after the COVID-19 pandemic started on February 23, 2020, when Korea's COVID-19 crisis alert level was raised to severe.

### Study setting

The emergency medical centers (EMCs) in Korea have three emergency levels: regional EMCs (REMCs), local EMCs (LEMCs), and local emergency medical agencies (LEMAs). Conceptually, this is a sequential emergency medical delivery system that treats the most serious patients at REMCs and moderate or mild emergency patients at regional institutions, including LEMCs and LEMAs. According to the Emergency Medical Service Act, Korea is divided into 29 emergency medical regions in accordance with residential areas, and 38 REMCs were in operation in January 2021. The minimum requirements for emergency medical resources, including human resources and isolation rooms, were specified according to the EMC level. LEMAs do not need isolation rooms; LEMCs must have at least one negative-pressure isolation room and two isolation rooms; and REMCs must have at least two negative-pressure isolation rooms and three isolation rooms.

Gyeonggi Province, located in the western central part of the Korean Peninsula, borders the west coast and surrounds the capital city of Seoul. It covers an area of 10,188 km<sup>2</sup> and has a population of 13.5 million as of 2020. Apart from the areas bordering

**Table 1.** Emergency medical resources of the four emergency medical regions in Gyeonggi Province

Variable	Emergency medical region			
	Northeast	Northwest	Southeast	Southwest
Population	986,013	2,047,474	2,620,071	4,003,388
No. of LEMAs	6	2	5	7
No. of LEMCs	1	6	5	9
No. of REMCs	1	1	2	2
Total no. of ED beds per 100,000 population				
2019	134 (13.6)	234 (11.4)	232 (8.9)	402 (10.0)
2020	138 (14.0)	230 (11.2)	275 (10.5)	402 (10.0)
Total no. of ED isolation rooms per million population				
2019	9 (9.1)	21 (10.3)	21 (8.0)	37 (9.2)
2020	10 (10.1)	24 (11.7)	29 (11.1)	49 (12.2)

LEMA, local emergency medical agency; LEMC, local emergency medical center; REMC, regional emergency medical center; ED, emergency department.

the other provinces, the remaining areas were divided into four emergency medical regions: northeast, northwest, southeast, and southwest (Supplementary Fig. 1). Table 1 shows the emergency medical resources for each of the four emergency medical regions in Gyeonggi Province. The population of each region was highest in the southwest region at 4,003,388 and lowest in the northeast at 986,013. The number of ED beds per 100,000 population was highest in the northeast region in 2019 and 2020, at 13.6 and 14.0, respectively. The number of ED isolation rooms per million population was highest in 2019 in the northwest region at 10.3 and highest in 2020 in the southwest region at 12.2.

The Korean EMS system, which is a government-operated system, provides basic-to-intermediate level ambulance services. Gyeonggi Province has the largest number of dispatches and transfers among the 119-service ambulances nationwide. A total of 263 ambulances were used, with 1,912 emergency medical technicians on active duty, including 1,145 level 1 emergency medical technicians and 589 nurses [13].

### Data source

This study used the EMS run sheet database published by Gyeonggi Data Dream [14]. The numbers of EMCs and isolation rooms by region were obtained using the data from the emergency medical portal of the National Emergency Medical Center (NEMC) as of December 31, 2020.

### Study population

All patients who used the 119 service in any of the four emergency medical regions in Gyeonggi Province during the study period were included. Cases lacking call time, dispatch time, scene arrival time, or return time were excluded.

### Main outcome

The call-to-return time (elapsed interval from the time of 119 call to return to station) was the primary outcome. The call-to-return time and the call-to-scene time were calculated using call time, scene arrival time, and return time as recorded on the EMS ambulance run sheet.

### Variables

The main exposures were the COVID-19 pandemic period and the number of ED isolation rooms in the region. The COVID-19 pandemic period was defined as any time after February 23, 2020. The total numbers of isolation rooms and beds in EMCs for each region were calculated by summing the number of quarantined rooms in the region reported to the NEMC. The numbers of isolation rooms and ED beds on December 31, 2019 were applied to

the data from January 1, 2019 to December 31, 2019. The numbers of isolation rooms and ED beds on December 31, 2020 were applied to the data from January 1, 2020 to December 31, 2020. Scene distance was defined as that between the dispatch site and the scene. The emergency medical region was defined according to the city where the patient was when they called 119. Occurrence place was categorized into private residence, group living or healthcare facility, or other public place based on the information in the ambulance run sheet. Patient symptoms, particularly fever and respiratory symptoms, were defined according to the chief complaints listed on the ambulance run sheet. Respiratory symptoms included dyspnea, cough, sputum, sore throat, and hemoptysis. Patients who were reported to be less than "alert" on the AVPU (alert, voice, pain, unresponsive) scale were defined as mentally altered.

### Statistical analyses

The differences before and after the COVID-19 pandemic period were compared using the chi-square test for categorical variables such as age group, sex, emergency medical region, out-of-area dispatch, foreigners, place, type of occurrence, symptoms, and altered mental status. Continuous variables such as age, scene distance, and time variables were described as medians and interquartile ranges, and the difference before and after the COVID-19 pandemic period was compared using the Wilcoxon rank-sum test.

To assess the effects of the COVID-19 period and regional ED isolation rooms on EMS travel time, two types of multivariable regression models were constructed. First, a generalized linear model (GLM) with a log link function and gamma distribution to fit skewed EMS travel times including call-to-return time and call-to-scene time was analyzed [15]. The exponential  $\beta$  coefficient [ $\exp(\beta)$ ] and 95% confidence interval for each effect variable were calculated in a univariable GLM. Multivariable GLMs with and without interaction terms were fit to estimate the effect of the COVID-19 period and the total number of isolation rooms in each region on the call-to-return time and call-to-scene arrival time and to adjust for the effects of confounders, including age, sex, number of ED beds, scene distance, call month, foreign nationality, fever, respiratory symptom, altered mental state, and trauma. The estimated  $\exp(\beta)$  for the number of isolation rooms per million population in each region in 2020 (northeast, 10.14; northwest, 11.72; southeast, 11.07; southwest, 12.24) was calculated. While the adjusted confounders were constant, the changes in call-to-return time during the COVID-19 period according to the number of isolation rooms per million population in 2020 in each region (northeast, 10.14; northwest, 11.72; southeast, 11.07; southwest, 12.24) are shown in an interaction

plot using the EFFECTPLOT statement in SAS ver. 9.4 (SAS Institute Inc.).

Second, a logistic regression model was analyzed to dichotomize cutoff values for call-to-return time (longer than 2 hours). Univariable and multivariable logistic regression models with an interaction term were fit to estimate the effect of COVID-19 according to the total number of isolation rooms in each region on the delayed call-to-return time. Confounders, including age, sex, number of ED beds, scene distance, call month, foreign nationality, fever, respiratory symptom, altered mental status, and trauma were adjusted. All statistical analyses were conducted using SAS ver. 9.4.

## RESULTS

Of the 929,044 EMS-assessed cases during the study period, 781,246 were included in the analysis after excluding cases with missing time variables (Fig. 1). Table 2 summarizes the demographic characteristics of the EMS-assessed patients before and after the COVID-19 pandemic. Before the pandemic started on February 23, 2020, there were a total of 463,570 cases, with a daily average of 1,109.0 cases. The number of cases during the

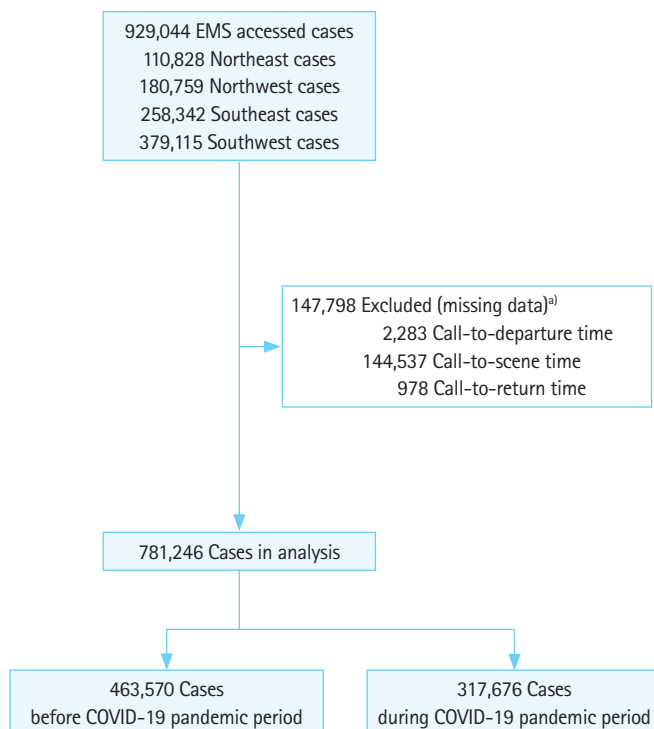
pandemic was 317,676 with a daily average of 1,014.9 cases. In both periods, the median age was 56 years, and the male proportion was 49.3% before the pandemic and 49.9% during the pandemic. There was no significant difference in the case volume by region before and after the pandemic. Among the main symptoms, fever (before 4.0% vs. after 4.5%,  $P < 0.05$ ) and respiratory symptoms (before 3.7% vs. after 4.4%,  $P < 0.05$ ) increased significantly during the pandemic. The call-to-departure time was 2 minutes in both periods. During the pandemic, the call-to-scene time (before 8 minutes vs. after 9 minutes,  $P < 0.05$ ) and call-to-return time (before 46 minutes vs. after 52 minutes,  $P < 0.05$ ) for emergency patients increased significantly.

Table 3 shows the change in EMS travel time during the pan-

**Table 2.** Baseline characteristics of study populations

Characteristic	Total	COVID-19 pandemic		P-value
		Before	During	
No. of cases	781,246	463,570	317,676	-
Daily no. of cases	1,068.7	1,109.0	1,014.9	-
Age (yr)	56 (37-72)	56 (37-72)	56 (38-72)	<0.01
< 18	49,839 (6.4)	32,587 (7.0)	17,252 (5.4)	
18-65	401,221 (51.4)	237,036 (51.1)	164,185 (51.7)	
> 65	240,564 (30.8)	142,098 (30.7)	98,466 (31.0)	
Sex				<0.01
Male	387,217 (49.6)	228,740 (49.3)	158,477 (49.9)	
Female	311,533 (39.9)	187,388 (40.4)	124,145 (39.1)	
Region				0.66
Northeast	95,557 (12.2)	56,568 (12.2)	38,989 (12.3)	
Northwest	154,982 (19.8)	92,132 (19.9)	62,850 (19.8)	
Southeast	214,600 (27.5)	127,288 (27.5)	87,312 (27.5)	
Southwest	214,600 (27.5)	127,288 (27.5)	87,312 (27.5)	
Out-of-area dispatch	108,411 (13.9)	64,739 (14.0)	43,672 (13.7)	<0.01
Foreign nationality	13,147 (1.7)	7,346 (1.6)	5,801 (1.8)	<0.01
Place				
Group living or healthcare facility	38,167 (4.9)	22,466 (4.8)	15,701 (4.9)	<0.01
Other public place	265,113 (33.9)	160,341 (34.6)	104,698 (33.0)	
Private place	414,099 (53.0)	242,026 (52.2)	172,073 (54.2)	
Type of occurrence				<0.01
Disease	528,442 (67.6)	300,200 (64.8)	228,242 (71.8)	
Injury	252,804 (32.4)	163,675 (35.2)	89,434 (28.2)	
Fever	32,940 (4.2)	18,675 (4.0)	14,265 (4.5)	<0.01
Respiratory symptom	31,171 (4.0)	17,100 (3.7)	14,071 (4.4)	<0.01
Altered mental status	62,644 (8.0)	35,988 (7.8)	26,656 (8.4)	<0.01
Scene distance (km)	2.0 (1.2-3.2)	1.9 (1.1-3.1)	2.0 (1.2-3.4)	<0.01
Call-to-departure time (min)	2 (1-3)	2 (1-3)	2 (1-3)	<0.01
Call-to-scene time (min)	9 (6-12)	8 (6-11)	9 (7-13)	<0.01
Call-to-return time (min)	48 (33-69)	46 (32-65)	52 (34-77)	<0.01
> 2 Hr	45,240 (5.8)	16,958 (3.7)	28,642 (9.0)	<0.01

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



**Fig. 1.** Flowchart of patient inclusion. EMS, emergency medical service.

<sup>a)</sup>15,271 Northeast cases (13.8%), 25,777 northwest cases (14.3%), 43,742 southeast cases (16.9%), and 63,008 southwest cases (16.6%).

**Table 3.** Emergency medical service travel time according to the period of COVID-19 by regions

Travel time	Northeast			Northwest			Southeast			Southwest		
	Before	After	P-value	Before	After	P-value	Before	After	P-value	Before	After	P-value
Call-to-departure (min)	2 (1–3)	2 (1–3)	<0.01	2 (1–3)	2 (1–3)	<0.01	2 (1–3)	2 (1–3)	<0.01	2 (1–3)	2 (1–3)	<0.01
Call-to-scene (min)	8 (6–11)	9 (7–13)	<0.01	8 (6–11)	10 (7–13)	<0.01	9 (6–12)	10 (7–14)	<0.01	8 (6–11)	9 (7–12)	<0.01
Call-to-return (min)	47 (33–66)	56 (38–84)	<0.01	44 (32–62)	53 (36–78)	<0.01	50 (34–71)	55 (36–83)	<0.01	43 (30–61)	48 (32–71)	<0.01

Values are presented as median (interquartile range).

**Table 4.** Effect of each variable on call-to-return time in the univariable generalized linear model

Variable	exp( $\beta$ )	95% Confidence interval	P-value
COVID-19	1.18	1.18–1.19	<0.01
COVID-19 <sup>a)</sup>	1.26	1.26–1.26	<0.01
Male sex	0.98	0.98–0.98	<0.01
Age (yr)			
< 18	1.00	Reference	
18–65	0.97	0.96–0.97	<0.01
> 65	1.11	1.11–1.12	<0.01
Scene distance	1.01	1.01–1.01	<0.01
No. isolation rooms per million population	1.03	1.03–1.03	<0.01
No. of ED beds per 100,000 population	1.02	1.02–1.02	<0.01
Fever	1.42	1.41–1.43	<0.01
Respiratory symptom	1.44	1.43–1.45	<0.01
Trauma	1.04	1.04–1.05	<0.01
Altered mental status	1.21	1.20–1.21	<0.01
Foreigner	1.18	1.18–1.19	<0.01
Place			
Private place	1.00	Reference	
Group living or healthcare facility	1.20	1.12–1.21	<0.01
Other public places	0.89	0.88–0.89	<0.01

exp( $\beta$ ), exponential  $\beta$  coefficient; ED, emergency department.

<sup>a)</sup>Generalized linear model in gamma distribution with log-link function adjusted to the number of beds in the ED, scene distance, call month, foreign nationality, fever, respiratory symptom, trauma, altered mental status and place without interaction term of COVID-19, and the number of isolation rooms per million population.

demic. In all four regions, call-to-departure time, call-to-scene time, and call-to-return time increased significantly compared with before the pandemic ( $P < 0.05$ ). During the COVID-19 pandemic, the median call-to-return time increased continuously, and the number of COVID-19 patients also increased continuously (Supplementary Fig. 2).

Table 4 shows the effect of each variable on the delay in EMS call-to-return time in the univariable GLM. During the pandemic, the call-to-return time increased by 1.18 times compared to that before the pandemic ( $P < 0.05$ ). For each increase in the number of isolation rooms in the region per million population, the call-to-return time increased by 1.03 times. It was also observed that fever, respiratory symptoms, and altered mental status increased

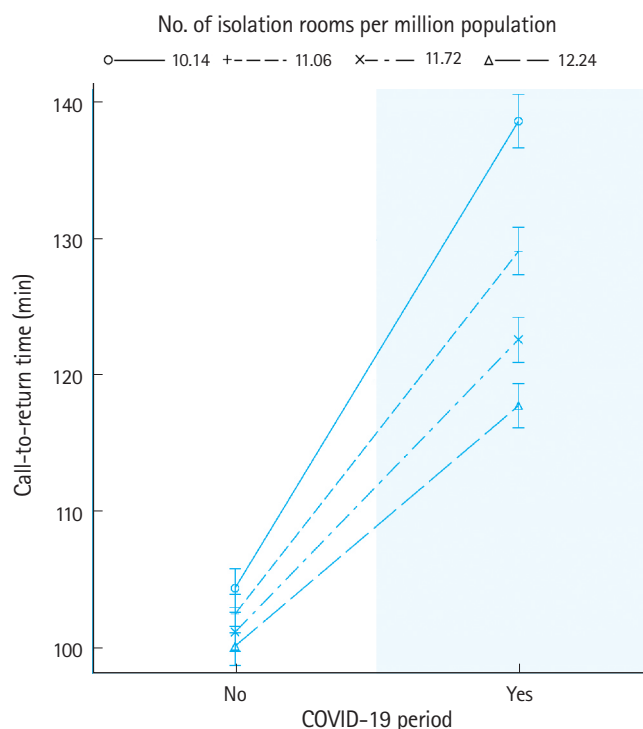
**Table 5.** Effect of COVID-19 period on call-to-return time in generalized linear model with interaction analysis of regional isolation room

Variable	exp( $\beta$ )	95% Confidence interval	P-value
Isolation room $\times$ COVID-19 (+)	0.94	0.94–0.95	<0.01
Isolation room $\times$ COVID-19 (–)	1.00		
COVID-19 at 10.14 isolation rooms per million population	1.33	1.32–1.33	<0.01
COVID-19 at 11.07 isolation rooms per million population	1.26	1.25–1.26	<0.01
COVID-19 at 11.72 isolation rooms per million population	1.21	1.21–1.22	<0.01
COVID-19 at 12.24 isolation rooms per million population	1.18	1.17–1.18	<0.01

Generalized linear model in gamma distribution with log-link function adjusted for the number of beds in the emergency department, scene distance, call month, foreign nationality, fever, respiratory symptom, trauma, altered mental status and place with interaction term of COVID-19, and the number of isolation room in region per million population.  
exp( $\beta$ ), exponential  $\beta$  coefficient.

the call-to-return time by 1.42, 1.44, and 1.21 times, respectively.

Table 5 shows the association between the pandemic and regional isolation rooms for the call-to-return time in a multivariable GLM. The number of regional isolation rooms had a statistically significant interaction effect with the COVID-19 period ( $P < 0.05$ ). As regional isolation rooms increased, the effect of COVID-19 on the call-to-return time decreased significantly in the multivariable GLM with interaction term (10.14 isolation rooms per million population: adjusted exp( $\beta$ ), 1.33; 12.24 isolation rooms per million population: adjusted exp( $\beta$ ), 1.18). The interaction plot in Fig. 2 shows that the delay in the call-to-return time during the pandemic was greater in regions with fewer isolation rooms. Supplementary Table 1 shows the association between the pandemic and the number of regional isolation rooms for call-to-scene time. As the number of regional isolation rooms increased, the effect of COVID-19 on the call-to-scene time decreased significantly in a multivariable GLM with an interaction term (10.14 isolation rooms per million population: adjusted exp( $\beta$ ), 1.20; 12.24 isolation rooms per million population: adjusted exp( $\beta$ ), 1.09). The interaction plot in Supplementary Fig. 3



**Fig. 2.** Interaction plot of the COVID-19 period and the number of isolation rooms per million population on call-to-return time. Fit computed: number of emergency department beds, 10.69; scene distance, 2.60 km; call month, 6.35; age group, >65 years; male sex; fever; altered mental status; respiratory symptom; trauma; occurred at other public place; foreign nationality.

shows that the delay in the call-to-scene time during the pandemic was greater in regions with fewer isolation rooms.

Table 6 shows the interaction effect between COVID-19 and region isolation rooms for delayed call-to-return time more than 2 hours. In the unadjusted logistic regression, the COVID-19 period increased the delayed call-to-return time by 2.67 times (odds ratio [OR], 2.67;  $P < 0.05$ ). COVID-19 had a significant interaction with the number of isolation rooms ( $P < 0.05$ ), and the effect of COVID-19 significantly decreased as isolation room number increased (10.14 isolation rooms per million population: OR 2.07,  $P < 0.05$ ; 12.24 isolation rooms per million population: OR 1.58,  $P < 0.05$ ).

## DISCUSSION

This study was conducted to analyze the effect of imbalance in the distribution of emergency medical resources between regions in the prehospital stage for people seeking emergency services during the COVID-19 pandemic. The call-to-return time and the call-to-scene time of emergency patients increased significantly overall during the pandemic. However, as the number of isolation

**Table 6.** Effect of regional isolation room and COVID-19 period on more than 2-hour call-to-return time with interaction analysis of regional isolation room

Variable	OR	95% CI	P-value
Isolation room × COVID-19 (+)	0.88	0.87–0.89	< 0.01
Isolation room × COVID-19 (–)	1.00		
COVID-19 at 10.14 isolation rooms per million population <sup>a)</sup>	2.07	2.03–2.11	< 0.01
COVID-19 at 11.07 isolation rooms per million population <sup>a)</sup>	1.84	1.80–1.76	< 0.01
COVID-19 at 11.72 isolation rooms per million population <sup>a)</sup>	1.69	1.65–1.73	< 0.01
COVID-19 at 12.24 isolation rooms per million population <sup>a)</sup>	1.58	1.53–1.63	< 0.01

In the univariable logistic regression model, the OR of COVID-19 period was 2.67 (95% CI, 2.62–2.72;  $P < 0.001$ ). In the multivariable logistic regression model adjusted for the number of beds in the emergency department, scene distance, call month, foreign nationality, fever, respiratory symptom, trauma, altered mental status and place with interaction term of COVID-19, and the number of isolation room in region per million population, the OR of COVID-19 period was 3.73 (95% CI, 3.59–3.87;  $P < 0.001$ ).

OR, odds ratio; CI, confidence interval.

<sup>a)</sup>Multivariable logistic regression model adjusted for the number of beds in the emergency department, scene distance, call month, foreign nationality, fever, respiratory symptom, trauma, altered mental status, and place.

beds in emergency rooms in regions increased, both the call-to-return time and the call-to-scene time showed a smaller increase during the pandemic.

Previous studies have reported an increase in the time required to visit the emergency room during COVID-19 [4,16], and consequently, patient prognoses for various diseases deteriorated [5,16–21]. Further, delayed patient arrival time to the hospital worsened prognosis for diseases such as stroke, myocardial infarction, and cardiac arrest [22–25]. In this study, we observed that the EMS call-to-return time significantly increased during the pandemic in Gyeonggi Province. The call-to-hospital-arrival time was not available, and it was not possible to determine whether the patient was directly delayed in transport. However, it could be estimated that the call-to-hospital arrival time increased as the call-to-departure time and the call-to-return time increased. According to previous studies, uneven distribution of emergency resources between regions affected patient prognosis [26–28]. This study shows that when the number of isolation rooms in a region is low, the call-to-return time increases during an infectious state of emergency.

Fever and respiratory symptoms are typical presentations of COVID-19 [11]. This study showed that the call-to-return time is significantly delayed for patients with fever or respiratory symptoms (Table 4). Not only the symptoms associated with COVID-19, but also the occurrence location and patient nationality were

significantly associated with delayed call-to-return time (Table 4). Cluster infections of COVID-19 have occurred in group living facilities like nursing homes and long-term care facilities [29]. Korea took measures to prevent COVID-19-infected people from entering the country since the beginning of the COVID-19 pandemic. This suggests that patient with suspected COVID-19 infection are more vulnerable to EMS access during the COVID-19 pandemic.

In this study, when the number of isolation rooms per million population was 10.14, the adjusted  $\exp(\beta_s)$  of COVID-19 was 1.33, and when the number of isolation rooms per million population was 12.24, the adjusted  $\exp(\beta)$  was 1.18. Therefore, the increase in call-to-return time during the pandemic was reduced by 7.1% with an increase of one isolation room per million population. After the outbreak of the Middle Eastern respiratory syndrome (MERS) coronavirus, an infectious disease disaster that occurred in Korea in 2015, the minimum number of isolation rooms needed in an emergency room was determined by the EMC level. According to the Emergency Medical Service Act, an LEMC must operate at least two isolation rooms. The Enforcement Decree of the Emergency Medical Service Act also mandates that the LEMC should provide one isolation bed per 500,000 people in each province. Thus, the difference of one isolation room per million population is estimated to be the effect size of 0.5 LEMC per million population; the added effect can be estimated as operation of 25% more LEMC compared with operation of the existing two LEMCs.

As shown in Table 1, the number of isolation beds per million population and the number of beds in emergency rooms per 100,000 population differ by region. In particular, the northeast region has the highest number of emergency beds but the lowest number of isolation rooms per capita. In Fig. 2, the call-to-return time and the call-to-scene time show the largest increase in this region during the COVID-19 pandemic. The difference between the number of ED beds versus isolation beds per population in the region is due to the lack of higher tier EMCs. The proportion of high-tier EMCs, more than LMCs, largely varies between regions (southeast, 58%; northeast, 25%; southwest, 61%; northwest, 78%). Lee [30] also noted an imbalance in the supply and demand of EMS when analyzing the spatial gap in Seoul, Korea. According to Yoo [31], most medical institutions in Korea are private and concentrated in urban areas. Therefore, there were relatively fewer high-tier EMCs in rural areas. Consequently, there was a lack of emergency medical resources such as isolation rooms. Thus, rural areas were more vulnerable to medical disasters like COVID-19. Therefore, it is necessary to reduce the imbalance of emergency medical resources between regions through investment in public hospitals.

This study had several limitations. First, it was conducted in a province in Korea, Gyeonggi Province, and the response protocol for COVID-19 was conducted differently depending on the available resources in each country and region, so it is difficult to generalize the results of this study. Second, the primary outcome of this study was call-to-return time, and it is difficult to estimate the actual patient's prehospital time because the call-to-hospital arrival time was omitted in this study. Therefore, there is a limitation to interpreting the results of this study as a prehospital time delay for patients during the COVID-19 pandemic. This study tried to interpret the primary outcome by focusing on the burden of the EMS to transport each patient. To analyze the effect of the number of isolation rooms on delay of initial medical access, the call-to-scene time was presented as a secondary outcome. Third, dynamic changes in health and medical policies of the government including social distancing during the pandemic and the change in the number of isolation rooms were not considered due to lack of data. By applying the annual number of isolation rooms and the number of ED beds, the difference between before and after COVID-19 was applied to the model to evaluate the regional response to COVID-19. Therefore, because the number of isolation rooms was calculated to have increased even in January and February 2020, before the pandemic, caution is needed when interpreting this study. Fourth, the differences between the regions were simplified by the number of isolation room and ED beds. The difference in medical accessibility according to geographic factors between regions was corrected using event-scene distance. However, it was not possible to precisely correct the differences in the distribution of emergency medical resources such as the EMS call volume and EMC tier between regions. However, according to the Korea Emergency Medical Act, the number of isolation beds in a region is determined by the EMC tier. Thus, this study reflected the difference in response to COVID-19 according to the level of emergency medical institutions in the region. Fifth, delayed EMS travel time was defined as an arbitrary criterion. The number of cases of delayed call-to-return time over 2 hours increased, but this does not provide additional information other than that average EMS travel time was delayed.

During the COVID-19 pandemic, the call-to-return time and call-to-scene time for emergency patients significantly increased. The greater was the number of isolation rooms among emergency rooms in a region, the smaller were the increases in call-to-scene time and call-to-return time. The lack of regional isolation rooms was associated with a delay in transfer during the prehospital stage and an increased burden for EMS.

## SUPPLEMENTARY MATERIALS

**Supplementary Table 1.** Effect of COVID-19 period on call-to-scene time in generalized linear model with interaction analysis of regional isolation room

**Supplementary Fig. 1.** Emergency medical region map of Gyeonggi Province.

**Supplementary Fig. 2.** Daily call-to-return time according to regions and COVID-19 patients in Gyeonggi Province.

**Supplementary Fig. 3.** Interaction plot of COVID-19 period and isolation room on call-to-scene time.

Supplementary materials are available from <https://doi.org/10.15441/ceem.22.355>.

## ETHICS STATEMENTS

This study was approved by the Institutional Review Board of Seoul Medical Center (No. SEOUL 2022-03-013). The need for informed consent was waived due to the retrospective nature of the study.

## CONFLICT OF INTEREST

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

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## AUTHOR CONTRIBUTIONS

Conceptualization: DSC; Data curation: SIL; Formal analysis: SIL; Investigation: SBK, DSC; Methodology: SYL; Project administration: DSC; Resources: SYL; Software: SYL; Supervision: DSC; Validation: DSC; Visualization: DSC; Writing—original draft: SIL, SBK; Writing—review & editing: SYL, DSC. All authors read and approved the final manuscript.

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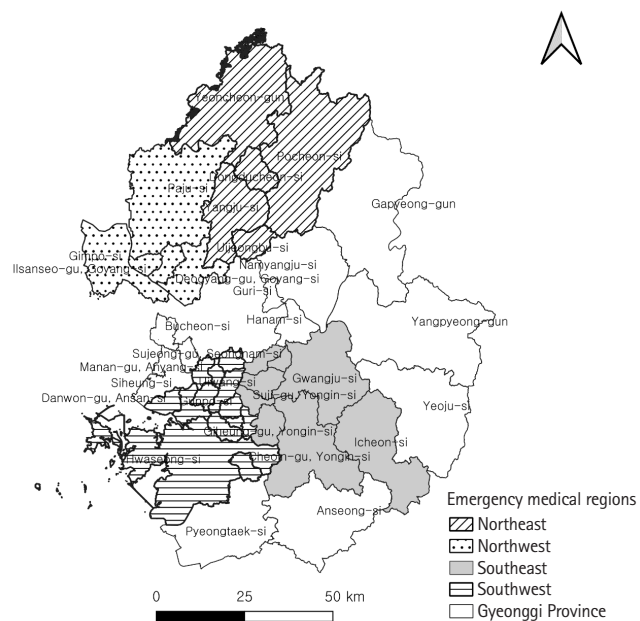
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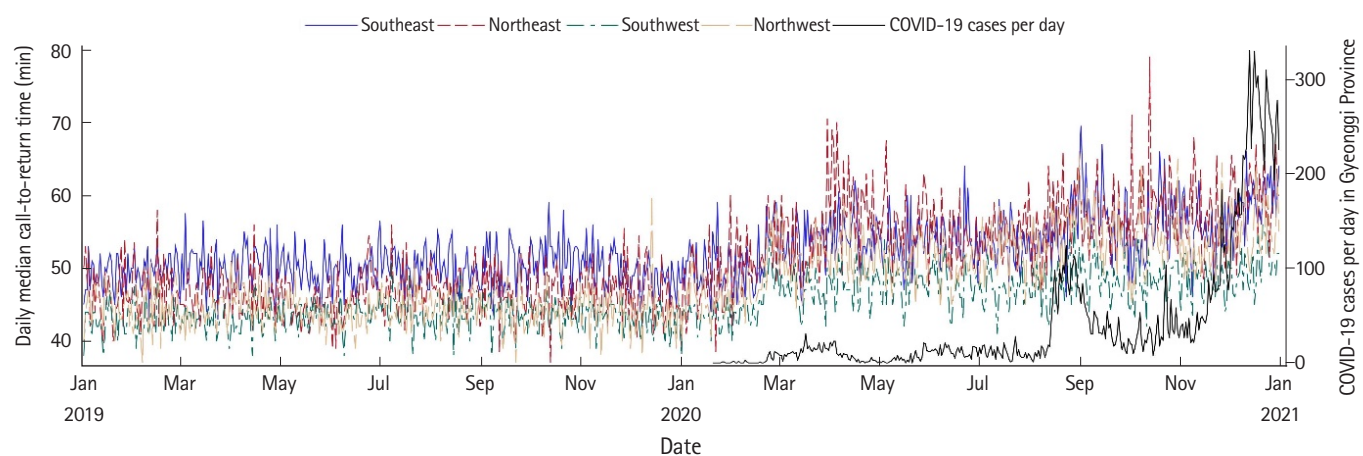
**Supplementary Table 1.** Effect of COVID-19 period on call-to-scene time in generalized linear model with interaction analysis of regional isolation room

Variable	Coefficient <sup>a)</sup>	95% Confidence interval	P-value
Isolation room × COVID-19 (+)	0.96	0.95–0.96	< 0.01
Isolation room × COVID-19 (–)	1		
COVID-19 at 10.14 isolation room per million population	1.20	1.20–1.20	< 0.01
COVID-19 at 11.07 isolation room per million population	1.15	1.15–1.15	< 0.01
COVID-19 at 11.72 isolation room per million population	1.12	1.11–1.12	< 0.01
COVID-19 at 12.24 isolation room per million population	1.09	1.09–1.10	< 0.01

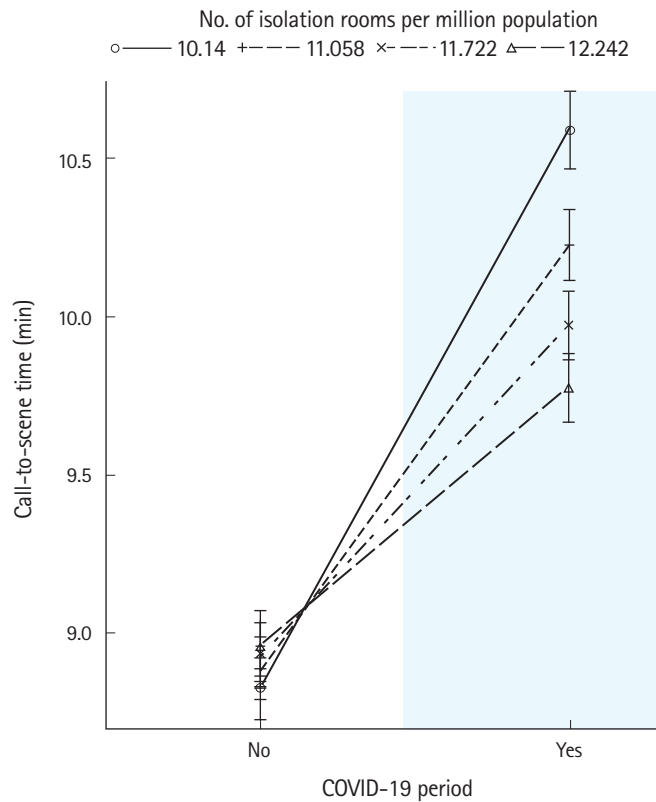
<sup>a)</sup>Generalized linear model in gamma distribution with log-link function adjusted for the number of beds in the emergency department, scene distance, call month, foreign nationality, fever, respiratory symptom, trauma, altered mental status and place with interaction term of COVID-19, and the number of isolation rooms in region per million population.



**Supplementary Fig. 1.** Emergency medical region map of Gyeonggi Province.



**Supplementary Fig. 2.** Daily call-to-return time according to regions and COVID-19 patients in Gyeonggi Province.



**Supplementary Fig. 3.** Interaction plot of COVID-19 period and isolation room on call-to-scene time. Fit computed: number of emergency department beds, 10.69; scene distance, 2.60 km; call month, 6.35; age group, >65 years; fever; altered mental status; respiratory symptom; trauma; occurred at other public place; foreign nationality.

# Chronic juvenile stress exacerbates neurobehavioral dysfunction and neuroinflammation following traumatic brain injury in adult mice

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**Objective** Chronic stress in adolescence may affect brain maturation and predispose individuals to psychiatric disorders in adulthood. However, whether chronic juvenile stress influences vulnerability to nonpsychiatric brain injuries, such as traumatic brain injury (TBI), remains unclear. Therefore, we hypothesized that juvenile stress-related neuronal circuit disturbances could aggravate brain damage following TBI in adulthood.

**Methods** For chronic stress, we used an unpredictable chronic mild stress (UCMS) procedure for 5 weeks in adolescent mice. This was followed by a controlled cortical impact (CCI) injury to evaluate the influence of chronic juvenile stress on brain damage progression following TBI in adult mice. Mice underwent UCMS alone, UCMS followed by CCI, CCI alone, or sham operation. We characterized neurobehavioral deficits (Barnes maze, open field, and light-dark tests), neuroinflammation (ionized calcium-binding adapter molecule 1 [Iba-1], glial fibrillary acidic protein [GFAP], and neuron-specific nuclear protein [NeuN] immunoreactivity), and apoptosis (B-cell lymph [Bcl-2], Bcl-2-associated X protein [Bax], and procaspase-3 immunoreactivity).

**Results** Following CCI, mice exposed to UCMS showed decreased spatial learning and memory in the Barnes maze test compared with unstressed mice. A significant increase in Iba-1, GFAP, and Bax/Bcl-2 immunostaining levels was observed in the mice exposed to UCMS followed by CCI compared with the CCI-only mice. In contrast, a significant decrease in NeuN immunostaining levels was observed in the UCMS with CCI group compared with the CCI alone group.

**Conclusion** Chronic stress in a juvenile mouse model aggravates neurobehavioral impairments and potentiates glial reactivity, neuronal injury, and apoptosis following moderate-to-severe TBI that occurs in adulthood. The present study suggests that juvenile chronic stress may influence poor outcomes following TBI in later adulthood.

**Keywords** Unpredictable chronic mild stress; Controlled cortical impact; Neuroinflammation; Neurobehavior

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## Capsule Summary

### What is already known

*Chronic stress in adolescence may affect brain maturation and predispose individuals to psychiatric disorders in adulthood.*

### What is new in the current study

*The present study demonstrated that juvenile chronic stress may influence poor outcomes following traumatic brain injury in later adulthood.*

## INTRODUCTION

Exposure to chronic stress can have broad effects on health, ranging from an increased predisposition to neuropsychiatric disorders such as anxiety, depression, and dementia to the dysregulation of immune responses [1]. Compared with adulthood, adolescence is a crucial developmental stage for continued brain maturation, particularly in the limbic and cortical regions, which play a role in the physiological and emotional changes coincident with adolescence [2]. A growing number of studies indicate that stressors experienced during adolescence may affect the trajectory of neural maturation and predispose individuals to the development of mental health problems such as anxiety and depression in adulthood [2–4]. Stress-related dysregulation of the neuroendocrine and immune systems in the development of the brain has been hypothesized as one of the major biological links between neuroinflammation and neurobehavioral dysfunction. During adolescence, exposure to psychosocial stress has been shown to upregulate inflammation by enhancing the transcription of proinflammatory genes such as interleukin-1 $\beta$ , interleukin-6, interleukin-8, cyclooxygenase 2, and tumor necrosis factor- $\alpha$ , as well as elicit increases in circulating levels of proinflammatory cytokines [5,6]. Through this mechanism, persistent stress may contribute to a chronic inflammatory environment, leading to negative downstream effects of adverse psychiatric events in adulthood. However, early life stress has demonstrated a clear association with psychological morbidities such as anxiety and depression in adulthood, but the impact of chronic stress during adolescence on non-psychological trauma in adulthood remains unknown.

Traumatic brain injury (TBI) is a major global public health concern and a common cause of morbidity and mortality [7]. TBI outcomes are affected by complex and multifactorial processes, including the heterogeneous nature of the human population, different injury types and severity, and the timing and characteristics of postinjury clinical care [8].

Chronic stress and TBI have overlapping pathophysiologies, such

as neuroinflammation and neurobehavioral abnormalities. Juvenile stress can affect normal neuronal maturation and increase psychological and physiological vulnerabilities downstream. We hypothesize that juvenile stress-related neuronal circuit disturbances can also influence significant neuronal injury vulnerabilities to nonpsychological neuronal stress, such as TBI. Therefore, TBI outcomes can be affected by chronic stress during adolescence.

Consequently, we investigated whether juvenile exposure to unpredictable chronic mild stress (UCMS) is associated with a more pronounced increase in neurobehavioral deficits and neuroinflammatory responses in mice exposed to nonpsychological neurotrauma with moderate-to-severe controlled cortical impact (CCI) during later adulthood.

## METHODS

### Ethics statements

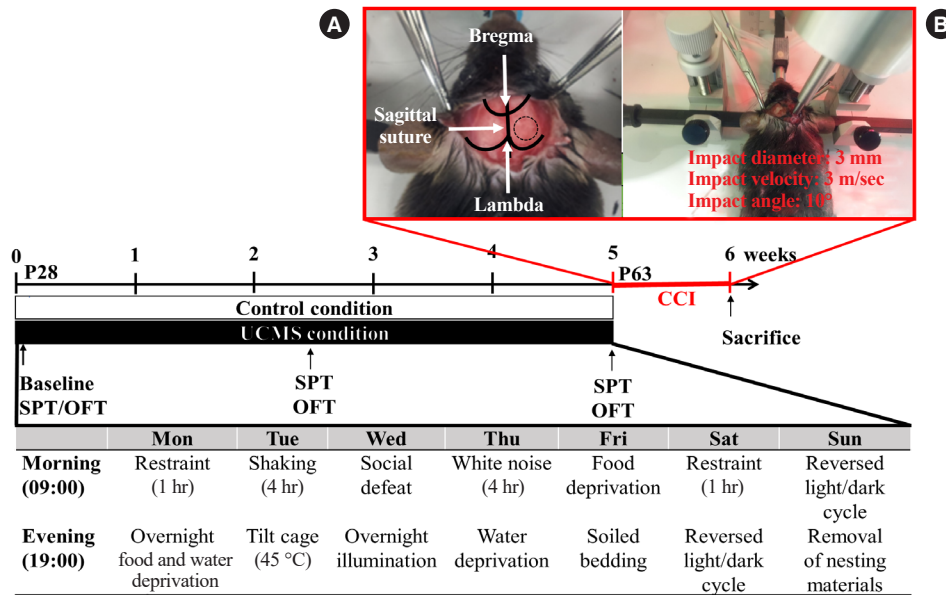
All experimental protocols were approved by the Animal Care and Use Committee of Chungbuk National University (No. CBNUR-854-15).

### Animal population

We used 8- to 12-week-old C57Bl/6 male mice in this study. Mice were housed under a standard 12-hour light-dark cycle and had *ad libitum* access to food and water. Mice underwent UCMS alone, UCMS followed by CCI, CCI alone, or sham operation.

### Unpredictable chronic mild stress procedure

In rodents, postnatal days 21 to 59 are commonly considered ages that are associated with adolescence [4]. The UCMS procedure was performed as described previously by Jung et al. [9] with slight modifications. Postnatal day 28 mice were subjected to different stressors such as restraint, shaking, social defeat, white noise, food deprivation, inversion of the light-dark cycle, food and water deprivation, cage tilting, damp sawdust, placement in an empty cage, and overnight illumination (Fig. 1). On average, two of these stress-



**Fig. 1.** Experimental schedule. The unpredictable chronic mild stress (UCMS) protocol lasted 5 weeks. Before the UCMS procedure, baseline sucrose intake was measured. Once a week, sucrose intake and body weight were measured. After 5 weeks of UCMS or control conditions, controlled cortical impact (CCI) experiments were conducted. (A, B) The procedure for CCI. At the beginning of surgery (day 0), the mouse head was stably fixed on the stereotaxic frame with an ear bar and mouth bits. (A) The right skull was exposed, and a 4-mm circle was drawn in the center of bregma and lambda. The bone was removed by drilling to generate a window for impact. (B) The impactor tip was retracted and lowered to the surface of the exposed dura until contact was made. One week after the CCI experiments, mice were tested for neurobehavioral activity before being sacrificed. The brains were then collected for western blotting. SPT, sucrose preference; OFT, open field test.

ors were applied daily at different times following a semi-random 2-week schedule. The stress procedure lasted for 5 weeks before behavioral testing. Stressors were applied during the testing phase, except on the testing days, to avoid the effects of acute stress. At least 12 hours of rest was provided between the stressor and the test.

### Sucrose preference test

The sucrose preference test was performed as described previously by Zhang et al. [10] with slight modifications to evaluate anhedonia. This test was carried out before UCMS, as well as 2.5 and 5 weeks after UCMS. Mice were kept individually in separate cages and allowed to adapt to two bottles of solution (filled with 1% sucrose solution) for 24 hours. For the next 24 hours, one bottle of sucrose solution was replaced with water. The mice were then subjected to 18 hours of food and water deprivation, followed by exposure to two preweighed bottles of solution (1% sucrose solution and plain water) for 1 hour. The positions of the bottles were then changed. After the test, the weights of the sucrose solution and water consumed were recorded. Sucrose preference was calculated as follows: sucrose preference (%) = sucrose consumption / (sucrose consumption + water consumption) × 100%.

### Controlled cortical impact

CCI was performed as described previously [11,12]. Briefly, mice were anesthetized with an intramuscular injection of 15 mg/kg tiletamine/zolazepam (Zoletil, Virbac). After cleaning the shaved head area between the ears with betadine, a midline scalp incision was made, and the right parietal bone was exposed. Next, a 4-mm-diameter circle was drawn in the center of Lambda and Bregma at 0.5 mm from the midline. Thereafter, right parietal craniotomy was carefully performed along the marked circle using a surgical microscope and micromotor drill (Stoelting). Afterward, the CCI device was calibrated relative to the exposed dura mater during craniotomy. The parameters of impact in the injured animals were a depth of 2.0 mm, a mean velocity of 3.0 m/sec, and a duration of 500 milliseconds. After the impact, the scalp incision was sutured with 5-0 nylon. The animals were then returned to their cages. The sham-operated group underwent craniotomy without CCI injury. The surgical procedure is illustrated in Fig. 1.

### Behavioral testing

Behavioral testing was conducted between 8 AM and 7 PM by an observer blinded to the experimental procedures. All tests were recorded using a video tracking system equipped with Smart ver. 3.0 (Harvard Apparatus, Holliston, MA, USA), which automatically

identifies postinjury behavioral changes.

### Barnes maze test

The Barnes maze test was conducted as previously described with minor modifications to determine latencies and distances, errors, and speed to find the escape box [11–13]. The maze consisted of a white acrylic circular platform (diameter, 91 cm) with 20 equally spaced holes and a black acrylic escape box (20 × 5 × 6 cm) along the perimeter. The maze was surrounded by four spatial cues at its height.

### Acquisition trials

Each mouse was trained by way of four acquisition trials per day over 3 days with an intertrial interval of 10 to 15 minutes. Immediately before the first trial, a mouse was placed in the middle of the maze in a black starting cylinder (diameter, 10 cm), and a buzzer (80–90 dB) was turned on. After 10 seconds, the chamber was lifted, and the mouse was pretrained to enter the escape box by guiding it to the escape box and allowing it to remain there for 2 minutes. The first trial was initiated following the pretraining trial.

At the beginning of each trial, a mouse was placed in the same starting chamber, and 10 seconds after turning on the buzzer and light, the chamber was lifted, and the mouse was free to explore the maze. The trial ended when the mouse entered the goal tunnel or 3 minutes into the trial. Immediately after the mouse entered the tunnel, the buzzer was turned off and the mouse was allowed to stay in the tunnel for 1 minute.

After each trial, the entire maze was cleaned with 70% alcohol and rotated to eliminate intramaze cues. The trials were recorded using a video tracking system equipped with Smart ver. 3.0.

### Probe trial

During the probe trial, the escape tunnel leading to the target box was closed. The 90-second probe trial was conducted on day 6, and the mice were allowed to explore the maze and visit the target hole. The latency and distance to reach the target hole were recorded for the first time.

### Open field test

Locomotor activity was measured in a white open-top acrylic box (40 × 40 × 40 cm) with an illumination intensity of 20 lux at the box floor level for 30 minutes. The activity was automatically recorded using a video tracking system equipped with Smart ver. 3.0. Distance moved (mm), time spent in the center (25%), time spent in the area margins, and mean walking speed (cm/sec) were also evaluated.

### Light-dark transition test

The apparatus consisted of black (20 × 40 × 40 cm) and white compartments (20 × 40 × 40 cm) separated by a connecting gate (5 × 8 cm). Each animal was individually placed at the center of the bright compartment (facing away from the door), and the following parameters were measured for 5 minutes: latency of the initial movement from the light to the dark area (latency of transition), the total number of transitions between the light and dark areas, and total time spent in the light area.

### Western blotting

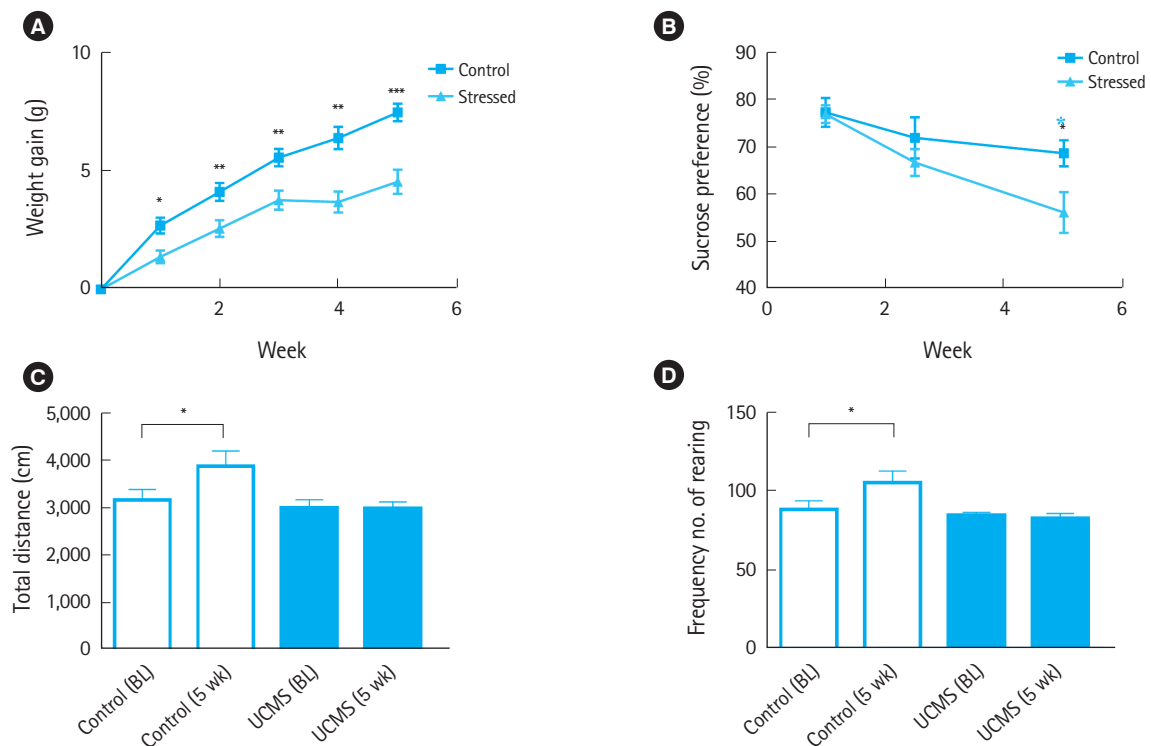
Seven days postinjury, the animals were sedated with an intramuscular injection of 15 mg/kg tiletamine/zolazepam (Zoletil) and sacrificed. Brain tissue (three to four in each group) was dissected and stored at –80 °C immediately before use. The samples were lysed with ice-cold radioimmunoprecipitation assay buffer (#MB-030-0050, Rockland) supplemented with 10 µL/mL protease and phosphatase duo inhibitor cocktail (#P3300-001, GenDEPOT) and homogenized using a syringe with a 23G needle (approximately 10 to 20 times) at room temperature (RT). The tissue lysates were incubated on ice for 30 minutes and mixed using a vortex device every 5 minutes. The supernatants were collected after centrifugation at 13,000 rpm at 4 °C for 10 minutes. The Bradford assay method (#5000202, Bio-Rad Laboratories) was used to measure the protein concentration of the samples. After protein quantification, each sample was treated with 4× Laemmli sample buffer (#161-0747, Bio-Rad Laboratories) containing 10% (volume/volume) β-mercaptoethanol (#M3148, Sigma-Aldrich). After boiling in a dry bath at 95 °C for 10 minutes, the samples were stabilized on ice for 5 minutes and centrifuged at 13,000 rpm and 4 °C for 10 minutes. Next, the supernatants (10 µg in a 4-, 7.8-, 10-, or 13.4-µL volume) were separated using Any kD Mini-PROTEAN TGX Precast Protein Gels (#456-9034, Bio-Rad Laboratories) and sodium dodecyl sulfate-polyacrylamide gel electrophoresis (#165-8004, Bio-Rad Laboratories) at a constant voltage of 200 V for 35 minutes, and then transferred to a 0.45-µm (#10600023, Amersham) or 0.2-µm (#10600021, Amersham) pore size hydrophobic bond polyvinylidene fluoride transfer membrane using a wet-tank (#TE22, Hoefer Inc) transfer method at 250 mA for 60 minutes. Thereafter, the membranes were incubated with 15 mL of 5% (weight/volume, w/v) bovine serum albumin (BSA; #A0100-010, GenDEPOT) in Tris-buffered saline with Tween 20 (TBS-T) and 0.1% Tween-20 (#274348, Sigma-Aldrich) in 1× TBS buffer (#TR2008-100-00, Biosesang) to block nonspecific reactions for 2 hours at RT using a laboratory shaker (20 rpm; #AD-ST, GYROZEN) and washed three times with 15 mL of TBS-T for 10 minutes at RT (40 rpm). After washing, the mem-

branes were incubated overnight at 4 °C with 10 mL of 5% (w/v) BSA in TBS-T containing an appropriate concentration of the primary antibodies against RNA-binding protein, including fox-1 homology 3/neuron-specific nuclear protein (RBFOX3/NeuN), glial fibrillary acidic protein (GFAP), allograft inflammatory factor 1/ionized calcium-binding adapter molecule 1 (AIF-1/Iba-1), B-cell lymphoma 2 (Bcl-2)-associated X protein (Bax), Bcl-2, procaspase-3, and  $\beta$ -actin for 18 to 24 hours, and then three times rinsed with 15 mL of TBS-T for 10 minutes at RT. After washing, the membranes were incubated with 15 mL of 5% (w/v) BSA in TBS-T, including horseradish peroxidase-conjugated secondary antibodies: goat anti-rabbit (1:3,000; #170-6515, Bio-Rad Laboratories) or goat anti-mouse (1:3,000; #170-6516, Bio-Rad Laboratories) polyclonal antibodies, for 1 hour at RT (20 rpm), and then washed three times with 15 mL of TBS-T for 10 minutes at RT. After washing, the bands were visualized using Clarity Western enhanced chemiluminescence Substrate (#170-5060, Bio-Rad Laboratories) and a ChemiDoc XRS+ Imaging System (#170-8265, Bio-Rad Laboratories) according to the manufacturer's protocol. Then, protein bands were analyzed quantitatively using ImageJ ver. 1.53k (US National Institutes of Health), and the results were used for further statistical analysis. The expression levels of the target protein

in the cortex of mice were determined relative to  $\beta$ -actin as an internal loading control, and all relative band intensities of target protein were normalized to the mean relative band intensity of the control and sham groups.

### Statistical analysis

All data are presented as the mean  $\pm$  standard error of the mean and, to ensure data accuracy, all western blot studies were repeated three to six times. GraphPad Prism ver. 9.3.1 (GraphPad Software) was used to analyze the normalized data and construct histograms. After using the Shapiro-Wilk and Brown-Forsythe tests to confirm data normality and homogeneity of variances, respectively, a two-way (stress, control vs. UCMS; UCMS  $\times$  operation, sham vs. TBI) analysis of variance (ANOVA) was used to analyze the effects of stress and brain damage. After the ANOVA verified the interaction effect ( $P < 0.05$ ) between stress and the operation, Tukey's (equal sample size) or Bonferroni's (unequal sample size) post hoc multiple comparison test was used to analyze the differences between groups. In the post hoc test for the western blot analysis, a value of  $P < 0.05$  was considered statistically significant.



**Fig. 2.** Weight gain, sucrose preference, and locomotor activity in control and unpredictable chronic mild stress (UCMS) groups. (A) Changes in body weight. (B) Sucrose preference in a time-dependent manner. (C) The total distance traveled in the open field test. (D) Frequency of rearing. All data are presented as mean  $\pm$  standard error of the mean ( $n=12$ ). BL, baseline. \* $P < 0.05$ . \*\* $P < 0.01$ . \*\*\* $P < 0.001$ .

## RESULTS

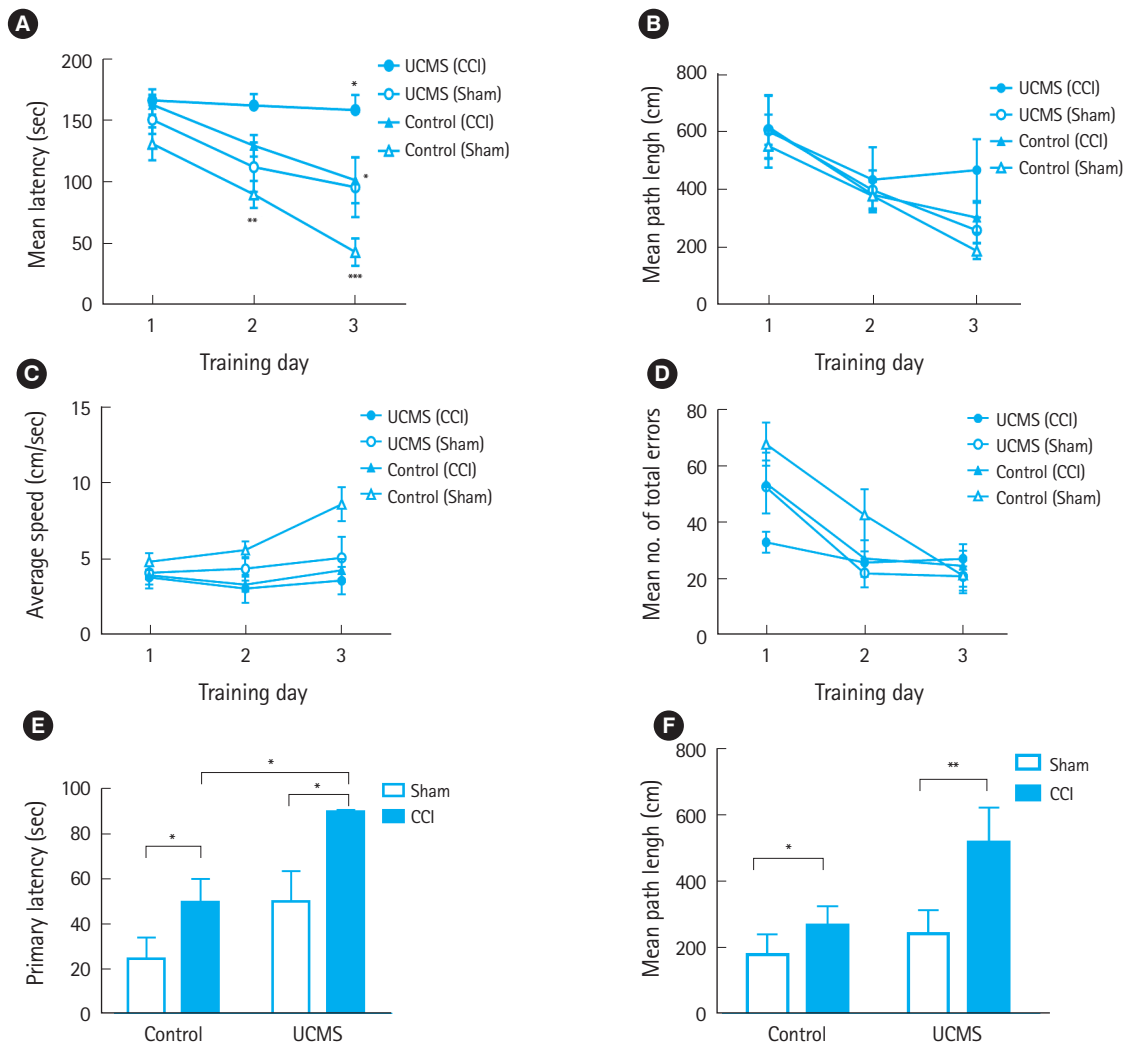
### UCMS reduced body weight gain, sucrose preferences, and locomotor activity

As illustrated in Fig. 2, body weight gain, sucrose preference, and locomotor activity were monitored to control for stressor efficacy. Before stress exposure, body weight gain did not differ significantly between the control and stress groups. However, stressed animals exhibited a reduction in body weight gain compared with controls after 1 week of stress exposure ( $0.8 \pm 0.4$  g vs.  $2.7 \pm 1.2$  g,  $P < 0.05$ ). After 5 weeks of UCMS, body weight gain in the stress group was significantly lower than that in the control group ( $3.0 \pm 1.5$  g vs.  $6.9 \pm 2.8$  g,  $P < 0.001$ ). Sucrose preference was similar between the two groups before stress exposure and after 2.5 weeks

of UCMS. However, after 5 weeks of UCMS, stressed animals exhibited a significant decrease in sucrose preference ( $56.1\% \pm 10.5\%$  vs.  $68.1\% \pm 18.4\%$ ,  $P < 0.05$ ). In the open field test (OFT), total ambulation and rearing time significantly increased ( $P < 0.05$ ) in control mice after 5 weeks, whereas stressed mice did not show a significant increase in total ambulation and rearing time.

### UCMS in adolescence alters neurobehavioral responses following TBI in adulthood

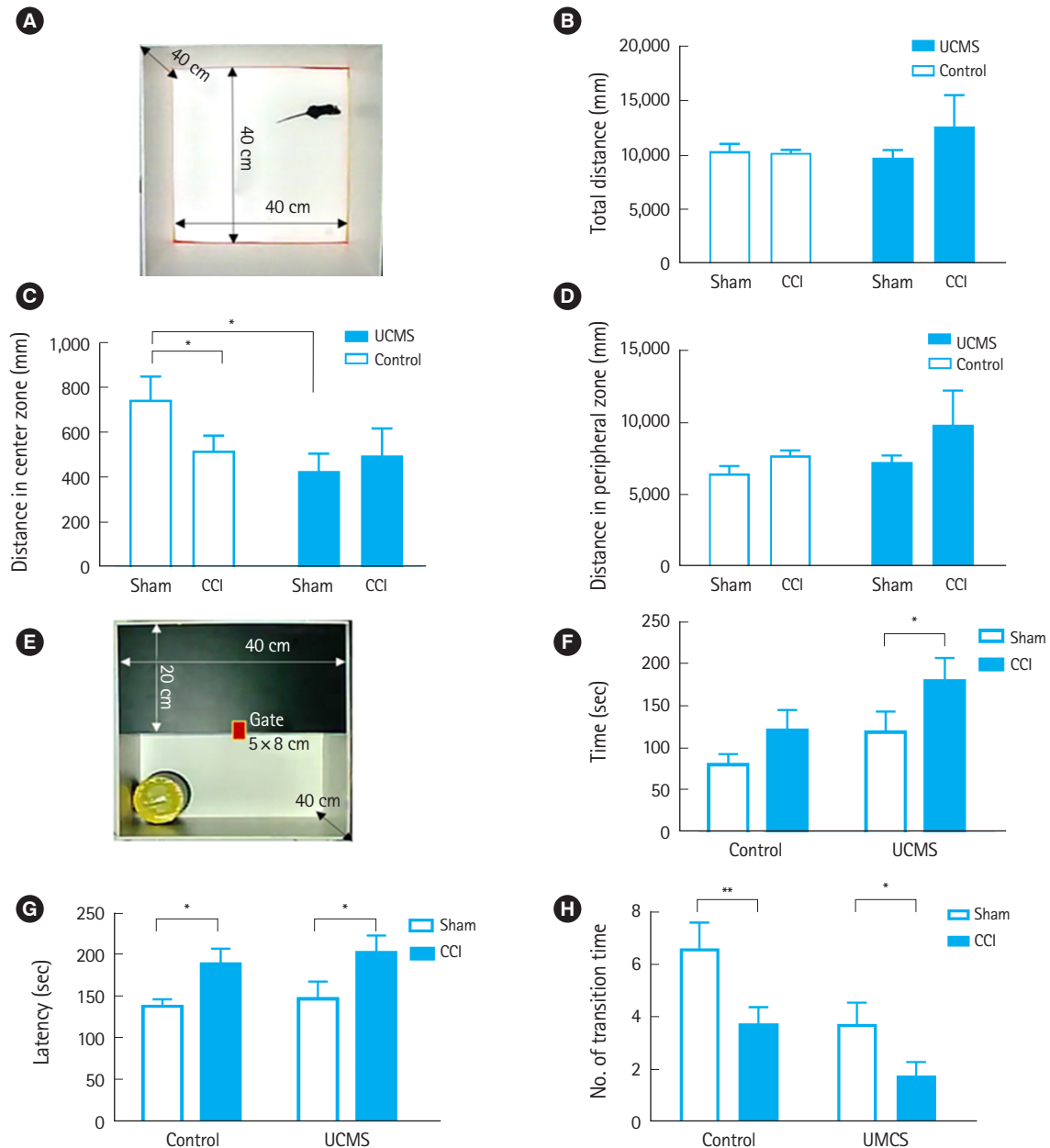
To analyze the influence of juvenile stress on spatial learning and memory deficits following TBI, we performed a Barnes maze test. During the training days, the latency (sec) to enter the target hole (total latency) was measured and analyzed using a two-way ANOVA. Nonstressed sham rats showed a significant decrease in la-



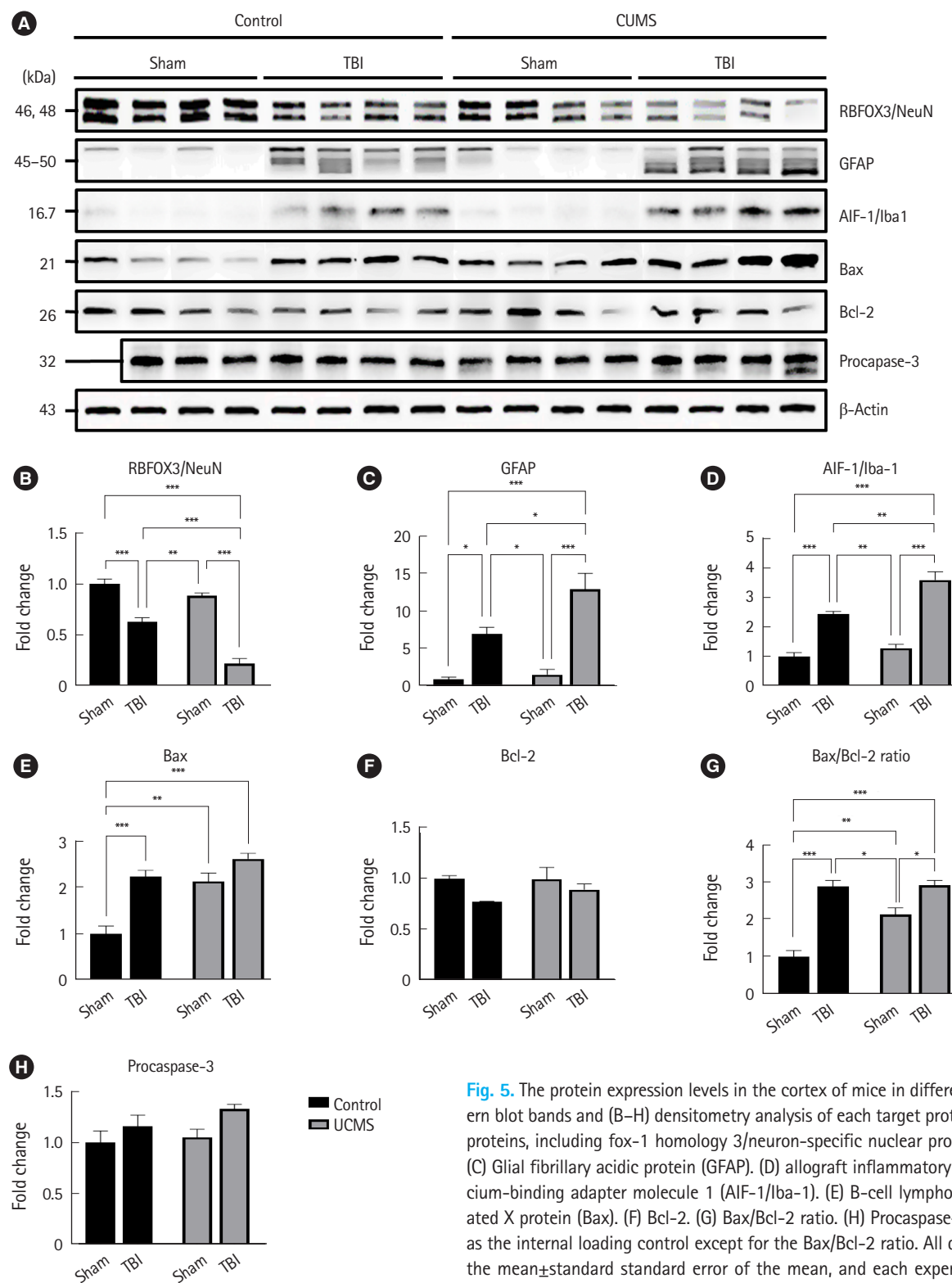
**Fig. 3.** Spatial learning and memory of animals following traumatic brain injury in control and unpredictable chronic mild stress (UCMS) group. (A) Mean latency (seconds) in acquisition trials. (B) Mean path length (cm) in acquisition trials. (C) Average speed in acquisition trials. (D) Mean total errors in acquisition trials. (E) Mean latency (seconds) in retention trials. (F) Mean path length (cm) on day 5 of retention trials. CCI, controlled cortical impact. \* $P < 0.05$ . \*\* $P < 0.01$ . \*\*\* $P < 0.001$  ( $n = 6$  to  $8$  per group, bars and whiskers represent mean  $\pm$  standard error of the mean).

tency during the 3 training days, indicating that they learned the task over the 3-day training period (Fig. 3A). However, mice that were subjected to TBI spent more time in the arena than those in the other groups (Fig. 3A). There was no significant difference in mean path length, average speed, and mean total errors among groups in the acquisition trials (Fig. 3B–D). The mean path length (cm) on day 5 of the retention trials in the retention phase, the

mean latency, and the path length to the target stress during the Barnes maze performance were affected by TBI and/or chronic stress. Unpaired t-test demonstrated statistically significant differences in primary latency to the target hole and adjacent holes between nonstressed mice following TBI and stressed mice following TBI, indicating that stressed mice following TBI had significant retention memory deficits (Fig. 3E). In addition, the pri-



**Fig. 4.** (A–D) Locomotor activity and anxiety-related behavior in mice following traumatic brain injury in control and unpredictable chronic mild stress (UCMS) group. (A) Schematic representation of the open field test. The typical running pathway record generated by tracking software shows the search paths and strategies of each group of mice. (B) Total distance moved. (C) Distance moved in the central zone. (D) Distance moved in the peripheral zone. (E–H) The light-dark transition test. (E) Schematic representation of the light-dark transition test. (F) Time spent in the lit compartment, (G) initial latency of transition, and (H) number of transition times in the light-dark box. Data were analyzed by two-way analysis of variance, followed by Tukey's post hoc test. CCI, controlled cortical impact. \* $P < 0.05$ . \*\* $P < 0.01$  ( $n = 8$  to 10 per group, bars and whiskers represent mean  $\pm$  standard error of the mean).



**Fig. 5.** The protein expression levels in the cortex of mice in different groups. (A) Western blot bands and (B–H) densitometry analysis of each target protein. (B) RNA-binding proteins, including fox-1 homology 3/neuron-specific nuclear protein (RbFOX3/NeuN). (C) Glial fibrillary acidic protein (GFAP). (D) allograft inflammatory factor 1/ionized calcium-binding adapter molecule 1 (AIF-1/Iba-1). (E) B-cell lymphoma 2 (Bcl-2)-associated X protein (Bax). (F) Bcl-2. (G) Bax/Bcl-2 ratio. (H) Procaspase-3.  $\beta$ -Actin was used as the internal loading control except for the Bax/Bcl-2 ratio. All data are presented as the mean  $\pm$  standard error of the mean, and each experiment was repeated more than three times ( $n=4$  in each group, but  $n=3$  in the procaspase-3 control+sham group). Statistical significance was analyzed by two-way analysis of variance (ANOVA). When an interaction effect occurred ( $P<0.05$  shown by ANOVA), Tukey's or Bonferroni's post hoc test was used to assess the difference between groups. CUMS, chronic unpredictable mild stress; TBI, traumatic brain injury. \* $P<0.05$ . \*\* $P<0.01$ . \*\*\* $P<0.001$ .

mary path length to the target hole was significantly greater in the difference between groups in stressed mice than in the difference between groups in unstressed mice (Fig. 3F).

To evaluate the influence of juvenile stress on anxiety-like behavior following CCI in adulthood, we performed the OFT and light-dark transition test (LDT). Fig. 4A depicts the OFT. As shown in Fig. 4B, the total locomotor activity was not influenced by TBI or chronic stress; however, the time spent in the central region of the testing chamber between nonstressed mice exposed to TBI and stressed mice was significantly reduced compared with that for nonstressed sham mice, indicating anxiety-like behavior, although the time spent in the peripheral region of the testing chamber among different groups was not significant (Fig. 4C, D). Fig. 4E shows a schematic representation of the LDT. After 2-mm CCI, stressed mice spent significantly more time in the light compartment than nonstressed mice (Fig. 4F). Mice exposed to TBI showed significant differences in the initial latency of transition (Fig. 4G) and transition time (Fig. 4H) compared with sham mice.

### UCMS in adolescence can potentiate neuronal injury and glial reactivity following TBI in adulthood

Although neuronal injury and glial reactivity did not differ significantly between the nonstressed and stressed sham groups, western blot analysis revealed that mice exposed to TBI had significantly different changes in neuronal injury and glial reactivity depending on whether they were stressed in adolescence.

Neurons are highly sensitive to traumatic injury. Neuronal injury and loss were evaluated by immunoblotting for NeuN, a neuronal-specific nuclear protein. Fig. 5A shows representative photomicrographs of NeuN western blotting in the injured cortex of each animal group. TBI caused a significant decrease in NeuN immunoreactivity compared with that in nonstressed and stress sham mice (Fig. 5B). Importantly, following TBI, the relative band intensity of NeuN in stressed mice decreased significantly more than that in nonstressed mice ( $P < 0.001$ ) (Fig. 5B).

To assess the effect of juvenile stress on astrogliosis following TBI, we immunoblotted GFAP. Fig. 5A shows representative images of GFAP western blotting in the injured cortex of each animal group. We found a significantly higher band intensity in the injured animals than that in both the nonstressed and stressed sham mice (Fig. 5C). Importantly, in the injured cortex, stressed mice had higher levels of GFAP than those in nonstressed mice after TBI ( $P < 0.05$ ).

To assess the contribution of microgliosis to TBI following juvenile stress, we performed immunoblotting for Iba-1, a macrophage/microglia-specific calcium-binding protein. Fig. 5A shows representative photomicrographs of Iba-1 western blotting in the

injured cortex of each animal group. Sham animals had very low levels of Iba-1 staining, with a marked increase in all groups following TBI (Fig. 5D). Stressed mice exposed to TBI exhibited a significant increase in Iba-1 staining compared with nonstressed mice, although there were no group differences between nonstressed and stressed sham mice.

Taken together, these findings suggest that in addition to primary neuronal loss due to TBI, secondary neuronal loss caused by chronic stress may occur in the penumbra connected to the damaged region through altered biochemical conditions, such as astrocyte and microglial overactivation, indicating that stressed mice are more vulnerable to secondary neuronal loss.

### UCMS in adolescence can enhance apoptosis following CCI

The levels of Bax and the Bax/Bcl-2 ratio, which are linked to biochemical circumstances in humans, also corroborate this statement. An increase in the Bax/Bcl-2 ratio indicates the probability of apoptosis in a tissue or specific region because Bax is a pro-apoptotic marker and Bcl-2 is an antiapoptotic marker. Levels of Bax were found to be considerably higher in either the stress-exposed or TBI-induced mice groups, or both (Fig. 5E). Additionally, the Bax/Bcl-2 ratio was significantly higher in both the stress-exposed and TBI-induced mice groups, or both (Fig. 5G). These findings suggest that apoptosis occurs under UCMS conditions and that this biochemical change with astrocyte and microglial activation may result in neuronal loss. Caspase-3 is an apoptosis executioner protein, and cleaved caspase-3 was used to evaluate caspase-3 activation as an essential apoptosis marker. However, using western blot analysis, we were unable to detect cleaved caspase-3 levels in these experiments (no data are shown in this study), and there was no interaction or significant difference in Bcl-2 and pro-caspase-3 levels between the groups (Fig. 5F, H).

## DISCUSSION

Our study shows for the first time that chronic stress in the developing brain exacerbates neurobehavioral dysfunction and neuroinflammatory responses in mice exposed to moderate-to-severe TBI that occurs in adulthood. We observed that chronically stressed juvenile mice showed a greater decrease in spatial learning and memory following TBI than nonstressed mice, indicating that chronic stress influences injury progression following TBI. Furthermore, our study identified that chronic juvenile stress could potentiate glial reactivity, neuronal injury, and apoptosis following moderate-to-severe TBI that occurs in adulthood, suggesting a prime factor influencing neuroinflammation following TBI in later adult-

hood.

Adolescence is a time of continued brain maturation, particularly in the limbic and cortical regions, which undoubtedly play a role in the physiological and emotional changes that coincide with adolescence [2]. Exposure to chronic stress in the developing brain can be particularly harmful and lead to more brain alterations and physiological disruptions that impact health and developmental outcomes throughout life than in adults because of vulnerability to the effects of chronic stress [14].

The UCMS rat model is a renowned rodent paradigm used to induce depressive-like and anxiety-like behaviors and consists of random, intermittent, and unpredictable exposure of animals to various stressful situations, usually for at least 4 weeks [1,15]. UCMS application during mouse adolescence induces long-term depressive-like susceptibility through impairment of the equilibrium of the hypothalamic-pituitary-adrenal axis and subsequent enhanced sympathetic activation, unbalanced reactivity, and hypercortisolemia, similar to the pathophysiology in humans [1,16,17]. UCMS is a potentially reliable model to explore the association of depressive-like behavior in mice with changes in peripheral pro-inflammatory cytokines, as well as neuroinflammation in various regions of the mouse brain known to be involved in the pathophysiology of depression [18].

In experimental animal models, juvenile stressed mice showed behavioral abnormalities such as increased anxiety-like behavior, decreased spatial memory, increased corticosterone secretion, and altered hippocampal size after maturation, resembling those seen in neuropsychiatric disorders and increased brain vulnerability [19]. We also observed that chronic mild stress in C57BL/6 juvenile mice induces a chronic stress response, as revealed by abrogated body weight gain, decreased sucrose preferences, and stress-associated behavioral alterations, including the potentiation of anxiety and depression-like behaviors and a reduction of exploratory behavior, as well as subtle stress-related changes in spatial learning and memory function in adulthood. The UCMS used in our study, first introduced by Katz et al. [20] and subsequently developed by Willner [16], is a renowned rodent paradigm applied to mice and rats in myriad studies to induce behavioral deficits such as anhedonia and behavioral despair [15,21]. During the procedure, adolescent animals were chronically exposed to various unpredictable mild stressors. One of the more prominent tests conducted following UCMS is the sucrose preference test, which is based on the rodents' innate preference for sweetened solutions rather than water and is widely acknowledged as an essential translational model for assessing anhedonia [15]. Other notable outcome measures that are highly incorporated in the UCMS literature are the OFT (measuring exploratory and anxiety-like behaviors and locomotor

activity) and the LDT (measuring anxiety-like behavior) as behavioral tests also applied in the present study [16].

Severe TBI presents with significant cognitive and/or affective dysfunction, which can have perpetual adverse consequences on the quality of life. Cognitive problems following TBI include decreased memory and learning abilities, impaired attention and concentration, reduced processing speed, word-finding difficulties, and impaired executive functioning [22]. Although the cognitive processes that result in memory impairment following TBI are not fully understood, alterations in neural circuits associated with memory function contribute to memory impairments caused by TBI [23]. We previously reported that a 2-mm CCI injury resulted in significant spatial learning and memory deficits compared with that in sham adults [11,12]. In previous studies, the Barnes circular maze was shown to be an efficient cognitive task to assess spatial/non-spatial learning following CCI injury in adult mice [11,12]. In addition to cognitive changes, TBI has been frequently linked to affective disorders such as anxiety and depression. However, much remains to be understood about the underlying molecular and signaling mechanisms that mediate affective dysfunctions following injury [24]. The evaluation of anxiety using the OFT and LDT in the present study showed differences in anxiety-like behaviors after CCI injury.

As described above, a growing body of experimental evidence indicates that chronic stress and TBI can lead to cognitive and affective dysfunction, respectively. We showed that juvenile mice exposed to chronic stress would likely suffer from spatial learning and memory dysfunction after TBI during adulthood relative to juvenile mice without chronic stress. In addition, behavioral alterations suggestive of anxiety-like and depression-like behaviors after TBI could be aggravated. It is unclear whether chronic stress and TBI have an overlapping effect on neurobehavioral dysfunction or whether chronic stress increases neuronal injury sensitivity to aggravate neuronal injury following TBI. However, the current study suggests that chronic stress during the juvenile period could contribute to secondary aggravating factors for neurobehavioral deficits following the same traumatic injury impact in adulthood.

To understand whether adolescent chronic stress accelerates the injury process after TBI, which worsens neurobehavioral abnormalities, we evaluated the extent of neuronal damage (loss of the NeuN signal), glial reactions (GFAP for astrocytes and Iba1 for microglia), and apoptotic reactions (Bax/Bcl-2 and procaspase-3). NeuN immunoreactivity has been widely used to identify live mature neurons in brain tissues and measure the neuron/glia ratio in brain regions. Reactive astrogliosis is a key component of cellular response to neuroinflammation. Astrocytic changes were evalu-

ated using an antibody against GFAP, a reactive astrocyte marker. Microglia are the main form of adaptive immune response in the central nervous system, which modulates neuronal function during inflammatory responses and developmental synaptic pruning and plasticity in the healthy brain, and can rapidly respond to even minor changes in the brain [25]. In response to harmful stimuli, microglial cells undergo several changes, such as an increase in the number of proinflammatory cytokines and the expression of several cell surface antigens [25–27]. Iba-1 has been widely used to study microglia because its expression is specific and is expressed by both reactive and quiescent microglial cells [27].

Neuroinflammation is a prominent short-term and long-term consequence of neuronal injuries that occur after TBI. It involves the activation of glia, including microglia and astrocytes, to release inflammatory mediators within the brain and subsequent recruitment of peripheral immune cells [28]. Various animal models of TBI have been developed that have proven valuable in elucidating the pathophysiology of the disorder and assessing the safety and efficacy of novel therapies before clinical trials [28]. These studies have reported a robust elevation of cytokines in brain homogenates after TBI [29]. Our data also show that TBI induces microglial and astrocyte reactivity and neural damage in ipsilateral brain homogenates that are altered by chronic stress.

There is consistent evidence that a range of psychosocial stressors during childhood leads to elevated microglial activity and proinflammatory cytokines in the hippocampus and other brain regions [25,30]. Such an elevated neuroinflammatory response may be associated with structural and functional changes in the brain that predispose it to a high risk of mental illness in adulthood. Alterations in the hypothalamic–pituitary stress system, abnormal immunological responses, and lasting changes in cellular, molecular, and epigenetic forms of plasticity have been proposed to explain the neurobiological pathways that link childhood adversities to the later development of adult mental illnesses [25]. Our data also showed that chronic stress induces microgliosis and astrogliosis in brain homogenates.

Our novel finding was that chronic stress enhances microglial and astrocyte reactivity induced by TBI. Diz-Chaves et al. [31] found that prenatal stress induces a basal proinflammatory status in hippocampal formation during adulthood, resulting in the potentiated activation of microglia and astrocytes in response to a subsequent proinflammatory insult. Similarly, another study found that combined exposure to prenatal immune challenge and peripubertal stress induces synergistic pathological effects on adult behavioral functions and neurochemistry, demonstrating that a prenatal insult markedly increases the vulnerability of pubescent offspring to brain immune changes in response to stress [32]. Such

studies support the idea that stress leads to microglial priming, whereby an initial stimulation early in life primes microglia, leading to an exaggerated response of microglia to a second inflammatory stimulus [25,33]. Although the findings of the two-hit hypothesis suggest that early life stress primes microglia, leading to a potentiated response to subsequent psychiatric stress, our results suggest that adolescent stress primes microglia, leading to an enhanced response to subsequent nonpsychiatric stress induced by TBI in adulthood.

This study has several limitations. First, we did not evaluate female mice or other mouse strains. Second, we did not analyze time-dependent protein expression early after injury. Third, we impacted the focal right parietal lobe; therefore, we need to further investigate other types of focal and diffuse brain injuries. Finally, we did not administer more than 2.0-mm impact owing to its high mortality rate after surgery.

In summary, our study shows for the first time that chronic stress in the developing brain exacerbates neuroinflammatory responses and neurobehavioral dysfunction in mice exposed to moderate-to-severe TBI that occurs in adulthood. Furthermore, the present study suggests that chronic juvenile stress primes neuroinflammation, leading to enhanced injury response to subsequent TBI.

## ETHICS STATEMENTS

All experimental protocols were approved by the Animal Care and Use Committee of Chungbuk National University (No. CBNUR-854-15).

## CONFLICT OF INTEREST

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

## FUNDING

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## AUTHOR CONTRIBUTIONS

Conceptualization: HK; Data curation: SJP; Formal analysis: SJP, HJP; Funding acquisition: HK; Visualization: HK, BK, YMK; Writing—original draft: HK, YMK; Writing—review & editing: all authors.

All authors read and approved the final manuscript.

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# Uncooperative patients suspected of acute stroke ineligible for prehospital stroke screening test by emergency medical service providers: final hospital diagnoses and characteristics

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**Objective** This study investigated the hospital diagnoses and characteristics of uncooperative prehospital patients suspected of acute stroke who could not undergo a prehospital stroke screening test (PHSST).

**Methods** This retrospective observational study was conducted at a single academic hospital with a regional stroke center. We analyzed three scenario-based prehospital stroke screening performances using the final hospital diagnoses: (1) a conservative approach only in patients who underwent the PHSST, (2) a real-world approach that considered all uncooperative patients as screening positive, and (3) a contrapositive approach that all uncooperative patients were considered as negative.

**Results** Of the 2,836 emergency medical services (EMS)-transported adult patients who met the prehospital criteria for suspicion of acute stroke, 486 (17.1%) were uncooperative, and 570 (20.1%) had a confirmed final diagnosis of acute stroke. The diagnosis in the uncooperative group did not differ from that in the cooperative group (22.0% vs. 19.7%,  $P=0.246$ ). The diagnostic performances of the PHSST in the conservative approach were as follows: 79.5% sensitivity (95% confidence interval [CI], 75.5%–83.1%), 90.2% specificity (95% CI, 88.8%–91.6%), and 0.849 area under the receiver operating characteristic curve (AUC; 95% CI, 0.829–0.868). The sensitivity and specificity were 83.3% (95% CI, 80.0%–86.3%) and 75.2% (95% CI, 73.3%–76.9%), respectively, in the real-world approach and 64.6% (95% CI, 60.5%–68.5%) and 91.9% (95% CI, 90.7%–93.0%), respectively, in the contrapositive approach. No significant difference was evident in the AUC between the real-world approach and the contrapositive approach (0.792 [95% CI, 0.775–0.810] vs. 0.782 [95% CI, 0.762–0.803],  $P>0.05$ ).

**Conclusion** We found overestimation (false positive) and underestimation (false negative) in the uncooperative group depending on the scenario-based EMS stroke screening policy for uncooperative prehospital patients suspected of acute stroke.

**Keywords** Emergency medical services; Stroke; Early diagnosis; Sensitivity and specificity

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## Capsule Summary

### What is already known

*Patients suspected of acute stroke can be medically unstable and uncooperative, and early stroke recognition in such patients is challenging in the prehospital setting. However, little is known about the prehospital evaluations of uncooperative patients suspected of acute stroke.*

### What is new in the current study

*The final diagnosis of acute stroke in the uncooperative group did not differ significantly from that in the cooperative group (22.0% vs. 19.7%,  $P=0.246$ ). We provide quantitative evidence of overestimation (false positive) and underestimation (false negative) in the uncooperative group depending on the emergency medical services stroke screening policy. In addition, prehospital factors (seizure at presentation, medical history of malignancy, clear onset of first abnormal time, systolic blood pressure  $<90$  mmHg, and absence of motor weakness of the upper extremities) were significantly associated with stroke mimics in the uncooperative group.*

## INTRODUCTION

Stroke is a leading cause of disability and death worldwide and is clinically described as a neurological deficit resulting from an infarction in the central nervous system (brain, spinal cord, and retinal cell death) that was caused by ischemia or hemorrhage (ischemic or hemorrhagic stroke, respectively) [1]. Approximately 795,000 individuals in the United States experience a stroke each year; of these, 87% are ischemic strokes, and 185,000 are recurrent strokes [2]. In Korea, approximately 105,000 people experience a new or recurrent stroke annually, and 76.3% of those are ischemic strokes [3]. In 2019, the Global Burden of Diseases, Injuries, and Risk Factors Study showed that stroke was the second most common cause of disability-adjusted life years in the 50 to 74 and  $>75$  years age groups [4]. With its high prevalence and tremendous burden on society, prevention, diagnosis, treatment, and rehabilitation of stroke survivors are essential parts of the public health agenda [5,6].

Stroke is a time-sensitive emergency, and emergency medical services (EMS) transport up to 70% of patients with stroke [7,8]. To achieve optimal outcomes in patients with stroke, it is crucial to minimize the interval from symptom onset to definitive treatment to restore blood flow to the stroke-affected tissue [9,10]. The EMS is the first point of contact in the prehospital phase of the stroke chain [11]. Therefore, rapid EMS activation and ambulance transport are recommended for patients with suspected stroke [12,13]. As a continuous process to reduce prehospital and in-hospital delays for acute stroke, this recommendation carries the advantage of allowing stroke screening and identification to be performed by the EMS providers even before hospital arrival [14].

Many prehospital stroke screening tools have been developed

to support the rapid and accurate recognition of stroke by EMS providers during their first contact. In fact, the use of prehospital stroke screening tools by EMS providers during their initial triage of patients with symptoms of stroke has been recommended internationally, with a positive screening result indicating a high suspicion of stroke that calls for urgent specialized assessments [15,16].

Sometimes, performing a prehospital stroke screening test (PHSST) is impossible because the patient suspected of having an acute stroke is uncooperative or medically unstable in the field. At present, the consensus under the Korean EMS policy is that uncooperative prehospital patients suspected to have acute stroke who cannot undergo a PHSST are considered to have a high stroke risk. However, studies of uncooperative prehospital patients suspected to have acute stroke are lacking, and prehospital evaluation performance is uncertain.

In this study, we investigated the final hospital diagnoses and characteristics of uncooperative prehospital patients suspected to have acute stroke who were transported by the EMS and unable to undergo a PHSST. Our secondary objective was to evaluate the scenario-based real-world performance of the current Korean EMS stroke screening policy for uncooperative prehospital patients suspected to have acute stroke.

## METHODS

### Ethics statements

This study was approved by the Institutional Review Board of Jeju National University Hospital (No. 2021-07-013). Informed consent was waived due to the retrospective nature of the study.

## Study design

This retrospective cross-sectional observational study was conducted at a single academic hospital from January 2015 to December 2019 to investigate the final hospital diagnoses and characteristics of uncooperative prehospital patients suspected to have acute stroke who were transported by the EMS and unable to undergo a PHSST.

## Study setting

This retrospective observational study was conducted at the single academic hospital possessing the only regional comprehensive stroke center (CSC) on Jeju Island, which has a population of approximately 670,000 citizens and an area of 1,833.2 km<sup>2</sup>. The prehospital EMS system on Jeju Island is a government-operated fire-based system with a mostly single-tiered intermediate service level. It comprises a single centralized dispatch center, 29 ambulances, and approximately 130 EMS providers. It possesses six emergency medical institutions (receiving facilities) and one CSC, which provides in-hospital services for acute stroke patients on Jeju Island.

The Korean EMS protocol for patients with suspected acute stroke follows the national EMS standards, which were based on the American Heart Association and the American Stroke Association recommendations for triage, treatment, transport, and documentation during the study period [17]. Under this protocol, the prehospital criteria for suspicion of acute stroke are non-traumatic patients older than 15 years with any of the following structured chief complaint codes: headache, dizziness, altered mental status, seizure, convulsion, syncope, motor weakness, sensory change, or other findings indicative of acute stroke. If a patient meets the prehospital criteria for a suspected acute stroke, EMS providers collect important information (apparent onset, last normal time, and first abnormal time [FAT]) and determine the Cincinnati Prehospital Stroke Scale (CPSS) as the PHSST. If the result of the CPSS is positive, the patient is classified as an EMS-assessed acute stroke case. All EMS-assessed acute stroke cases must be transported to the nearest CSC after prehospital notification.

If it is not possible to perform CPSS in a patient who is uncooperative or medically unstable, the patient is classified as an EMS-assessed acute stroke case.

## Data sources

Using EMS run sheets, EMS stroke registries, and hospital medical records from January 2015 to December 2019 as the data sources, we created a merged database for EMS-suspected acute stroke patients by manually linking the prehospital and hospital-phase

data for each patient. The EMS stroke registry, which was developed by the National Fire Agency in 2012, has been used for patients with suspected acute stroke on Jeju Island since 2015. In this registry system, the EMS provider is required to record the EMS run sheets, which contain basic but comprehensive information for all patients who are transferred by EMS ambulance, with additional mandatory records for all patients who meet the prehospital criteria for suspicion of acute stroke. To merge individual patient records from the EMS run sheets, EMS stroke registry, and hospital medical records, we reviewed the common identifiers (EMS call time, emergency department [ED] arrival time, sex, and age) and the context.

## Study population

Only adult patients who met the prehospital criteria for suspicion of acute stroke, were transported by the EMS to our ED and were registered in the EMS stroke registry between January 2015 and December 2019 were eligible for this study. Within that eligible population, patients for whom the EMS-assessed acute stroke case status or final clinical outcomes could not be determined from the EMS stroke registry or hospital record were excluded from the final analysis. The analyzed population contained participants aged 18 years or older at the time of the incident without other exclusion criteria and was divided into cooperative and uncooperative groups.

## Variables and measurements

We compiled and categorized the demographic and clinical information of the participants at both the prehospital and hospital phases: age, sex, chief complaint on EMS arrival (dizziness, altered mental status, seizure/convulsion, loss of consciousness, motor weakness, headache, dysarthria, facial palsy, and other), FAT (clear or unclear), activity at onset (work, sleeping, daily activities, and other), medical comorbidities (yes or no), prehospital mental status (alert, verbal, painful, and unresponsive), blood glucose test (performed or not), results of CPSS test (positive or negative), level of EMS provider (nurse, emergency medical technician [EMT]-intermediate, EMT-basic), ED disposition (discharge, admission, interhospital transfer, or death), and hospital diagnosis codes.

The hospital diagnoses for the participants were obtained from the electronic medical records (EMR) and were based on the World Health Organization's International Classification of Diseases 10th Revision (ICD-10) diagnosis codes [18,19].

## Main variables for diagnostic testing

The EMS-assessed stroke recognition is a binary item determined

by the results of the CPSS, which evaluates the presence of facial palsy, asymmetric arm weakness, and speech abnormalities. If any of the three items were marked positive, the EMS-assessed stroke recognition was positive.

The true diagnosis of the participants was considered the final hospital diagnosis. Therefore, we categorized three dichotomous indicators of acute stroke using the final hospital diagnosis ICD-10 codes: hemorrhagic stroke (ICD-10 diagnosis codes, I60.0–I62.9), ischemic stroke (ICD-10 diagnosis codes, I63.0–I63.9), and all strokes (ICD-10 diagnosis codes, I60.0–I64) [19].

We then evaluated the alternative diagnoses of patients in the uncooperative group whose final diagnoses did not contain ICD-10 codes for acute stroke. Two researchers independently reviewed the medical records and confirmed all final hospital diagnoses. The validated alternative diagnoses of the nonstroke patients in the uncooperative group were summarized based on a portion of their ICD codes (a single letter followed by the two digits that precede the period).

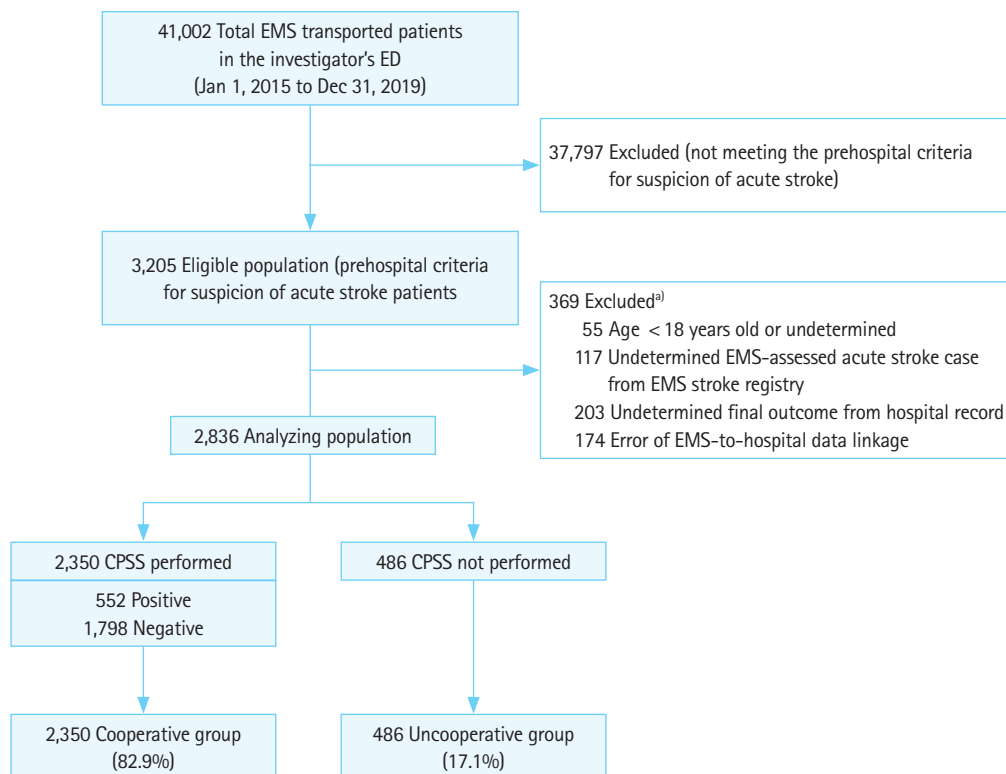
### Statistical analysis

Descriptive statistics are presented as frequencies and percentages for categorical variables and means with standard deviations

for continuous variables. Descriptive analyses between the cooperative and uncooperative groups were used to compare baseline demographic and clinical characteristics variables using Student t-test, chi-square test, or Fisher exact test as appropriate for the distribution. The performance (sensitivity, specificity, positive and negative likelihood ratios, positive predictive value [PPV], and negative predictive value [NPV]) of the EMS-assessed stroke recognition was evaluated for each of three scenarios using the final hospital diagnosis as the gold standard.

The first scenario used a conservative approach that calculated performance statistics only in patients who underwent the PHSST and excluded the uncooperative group. The second scenario used a real-world approach that considered all uncooperative patients as positive for EMS-assessed stroke recognition in calculating the performance statistics. The third scenario used a contrapositive approach, wherein all uncooperative patients were considered negative for EMS-assessed stroke recognition. We calculated the PPV and NPV with a stroke prevalence of 3% and compared the EMS stroke recognition performance in all three scenarios using the area under the receiver operating characteristic curve (AUC) [3].

To examine the prehospital factors associated with false-positive results in the uncooperative group, we performed univariate



**Fig. 1.** Flow diagram of patient enrollment. EMS, emergency medical services; ED, emergency department; CPSS, Cincinnati Prehospital Stroke Scale.

<sup>a)</sup>Inconsistent total due to overlapping cases.

and multivariate logistic regressions adjusted for age and sex. All statistical analyses were performed using Stata ver. 17.0 (Stata Corp), with a two-tailed test and a statistical significance level of <0.05.

## RESULTS

### Study flow

Among the 41,002 EMS-transferred patients who visited our ED during the study period, 3,205 met the prehospital criteria for suspicion of acute stroke and were registered in the EMS stroke registry. Of that eligible population, 369 patients were excluded for the following reasons with overlapping cases: 55 were younger than 18 years or their age was undetermined, 117 were undetermined EMS-assessed acute stroke cases from the EMS stroke registry, 203 had undetermined final clinical outcomes in the hospital records, and 174 had EMS-to-hospital data linkage errors. The final analyzed population of 2,836 participants contained 486 uncooperative patients (17.1%) and 2,350 cooperative patients (82.9%) (Fig. 1).

### Baseline demographics

The demographic and clinical characteristics of the uncooperative and cooperative groups are shown in Table 1. Of the 2,836 EMS-transported adult patients who met the prehospital criteria for suspicion of acute stroke, 570 (20.1%) had a confirmed final diagnosis of ischemic or hemorrhagic stroke; only the final diagnosis of hemorrhagic stroke was significantly higher in the uncooperative group than in the cooperative group (10.5% vs. 5.3%,  $P < 0.001$ ). The mean age of the participants in the uncooperative group was significantly higher ( $69.8 \pm 17.5$  years vs.  $63.7 \pm 17.5$  years,  $P < 0.001$ ). However, the proportions of female patients and medical comorbidities, except diabetes and stroke, were similar in the two groups. Clinical characteristics, such as the chief complaint at EMS arrival, FAT, and ED disposition, differed between the groups. The chief complaint of altered mental status (78.0% vs. 14.7%) was the most common complaint in the uncooperative group, whereas dizziness (43.6% vs. 1.9%) was the most common complaint in the cooperative group. In the uncooperative group, the FAT was more often unclear (37.9% vs. 18.7%,  $P < 0.001$ ), and symptoms were more likely to occur during sleep (21.6% vs. 14.5%,  $P < 0.001$ ).

### Accuracy analysis for each of the three scenarios

The sensitivity, specificity, positive and negative likelihood ratios, PPV, NPV, and AUCs for each of the three scenarios are summarized in Table 2. Among the 2,350 patients in the cooperative

**Table 1.** Baseline characteristics of EMS-transferred patients with suspected acute stroke

Characteristic	Total (n = 2,836)	Uncooperative (n = 486)	Cooperative (n = 2,350)	P-value
Age (yr)	64.8 ± 17.7	69.8 ± 17.5	63.7 ± 17.5	< 0.001
< 45	402 (14.2)	48 (9.9)	354 (15.1)	0.003
Female sex	1,381 (48.7)	250 (51.4)	1,131 (48.1)	0.184
Chief complaint at EMS arrival				< 0.001
Dizziness	1,034 (36.5)	9 (1.9)	1,025 (43.6)	
Altered mental status	725 (25.6)	379 (78.0)	346 (14.7)	
Seizure	273 (9.6)	50 (10.3)	223 (9.5)	
Loss of consciousness	173 (6.1)	18 (3.7)	155 (6.6)	
Weakness				
Upper extremity	254 (9.0)	8 (1.7)	246 (10.5)	
Lower extremity	60 (2.1)	2 (0.4)	58 (2.5)	
Headache	107 (3.8)	5 (1.0)	102 (4.3)	
Dysarthria	102 (3.6)	6 (1.2)	96 (4.1)	
Facial palsy	60 (2.1)	2 (0.4)	58 (2.5)	
Other	47 (1.7)	7 (1.4)	40 (1.7)	
First abnormal time				< 0.001
Clear	2,212 (78.0)	302 (62.1)	1,910 (81.3)	
Unclear	624 (22.0)	184 (37.9)	440 (18.7)	
Activity at onset				< 0.001
On duty	85 (3.0)	11 (2.3)	74 (3.1)	
Sleeping	446 (15.7)	105 (21.6)	341 (14.5)	
Daily activity	2,100 (74.1)	329 (67.7)	1,771 (75.4)	
Other activity	205 (7.2)	41 (8.4)	164 (7.0)	
Medical history				
Hypertension	1,089 (38.4)	174 (35.8)	915 (38.9)	0.196
Diabetes	591 (20.8)	118 (24.3)	473 (20.1)	0.040
Stroke	407 (14.4)	94 (19.3)	313 (13.3)	0.001
Cardiovascular disease	298 (10.5)	40 (8.2)	258 (11.0)	0.072
Malignancy	200 (7.1)	43 (8.9)	157 (6.7)	0.089
Blood glucose test (yes)	1,793 (63.2)	382 (78.6)	1,411 (60.0)	< 0.001
CPSS (positive)				
Facial palsy	296 (12.6)	NA	296 (12.6)	NA
Arm weakness	472 (20.1)	NA	472 (20.1)	NA
Dysarthria	417 (17.7)	NA	417 (17.7)	NA
Level of the EMS crew				0.964
Nurse	959 (33.8)	163 (33.5)	796 (33.8)	
EMT-intermediate	1,833 (64.6)	316 (65.0)	1,517 (64.6)	
EMT-basic	44 (1.6)	7 (1.4)	37 (1.6)	
ED disposition				< 0.001
Discharge	1,536 (54.2)	116 (23.9)	1,420 (60.4)	
Admission	1,235 (43.5)	342 (70.4)	893 (38.0)	
Interhospital transfer	50 (1.8)	20 (4.1)	30 (1.3)	
Death	15 (0.5)	8 (1.6)	7 (0.3)	
Final diagnosis (stroke) <sup>a)</sup>	570 (20.1)	107 (22.0)	463 (19.7)	0.246
Ischemic stroke	402 (14.2)	59 (12.1)	343 (14.6)	0.158
Hemorrhagic stroke	176 (6.2)	51 (10.5)	125 (5.3)	< 0.001

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

EMS, emergency medical services; CPSS, Cincinnati Prehospital Stroke Scale; NA, not applicable; EMT, emergency medical technician; ED, emergency department.

<sup>a)</sup>Eight patients were diagnosed with both ischemic and hemorrhagic strokes concurrently.

**Table 2.** Performance analysis of EMS-assessed stroke recognition for three scenarios

Parameter	Scenario 1 (conservative approach)			Scenario 2 (real-world approach)			Scenario 3 (contrapositive approach)		
	Positive	Negative	Total	Positive	Negative	Total	Positive	Negative	Total
Stroke	368	95	463	475	95	570	368	202	570
Stroke mimic	184	1,703	1,887	563	1,703	2,266	184	2,082	2,266
Total	552	1,798	2,350	1,038	1,798	2,836	552	2,284	2,836
Test characteristic									
Sensitivity (%)	79.5 (75.5–83.1)			83.3 (80.0–86.3)			64.6 (60.5–68.5)		
Specificity (%)	90.2 (88.8–91.6)			75.2 (73.3–76.9)			91.9 (90.7–93.0)		
Positive likelihood ratio	8.15 (7.05–9.42)			3.35 (3.09–3.64)			7.95 (6.83–9.25)		
Negative likelihood ratio	0.227 (0.190–0.272)			0.222 (0.184–0.267)			0.386 (0.345–0.431)		
Positive predictive value (%)	20.1 (17.9–22.6)			9.4 (8.7–10.1)			19.7 (17.4–22.2)		
Negative predictive value (%)	99.3 (99.2–99.4)			99.3 (99.2–99.4)			98.8 (98.7–98.9)		
AUC	0.849 (0.829–0.868)			0.792 (0.775–0.810)			0.782 (0.762–0.803)		

Values are presented as number or odds ratio (95% confidence interval).

EMS, emergency medical services; AUC, area under the receiver operating characteristic curve.

**Table 3.** Prehospital factors associated with stroke mimic in the uncooperative group

False-positive acute stroke	Odds ratio (95% CI)	Adjusted odds ratio <sup>a)</sup> (95% CI)
Age (yr)	0.99 (0.98–1.00)	–
Male sex	1.05 (0.68–1.61)	–
Chief complaint at EMS arrival		
Dizziness	2.29 (0.28–18.48)	2.16 (0.27–17.61)
Altered mental status	1.10 (0.66–1.84)	1.18 (0.70–1.98)
Seizure	3.56 (1.25–10.12)	3.27 (1.13–9.44)
Loss of consciousness	0.73 (0.25–2.08)	0.74 (0.26–2.12)
Weakness		
Upper extremity	0.09 (0.02–0.45)	0.10 (0.02–0.49)
Lower extremity	0.28 (0.02–4.52)	0.29 (0.02–4.67)
Headache	0.18 (0.03–1.12)	0.17 (0.03–1.05)
Dysarthria	0.28 (0.06–1.39)	0.26 (0.05–1.34)
Clear first abnormal time	2.26 (1.46–3.50)	2.33 (1.40–3.61)
Activity at onset	0.88 (0.61–1.26)	0.88 (0.61–1.28)
Medical history		
Hypertension	0.68 (0.44–1.05)	0.72 (0.46–1.14)
Diabetes	1.52 (0.89–2.60)	1.60 (0.93–2.76)
Stroke	0.78 (0.46–1.32)	0.83 (0.49–1.42)
Cardiovascular disease	0.72 (0.35–1.50)	0.79 (0.38–1.65)
Malignancy	4.09 (1.24–13.50)	4.36 (1.31–14.50)
Prehospital mental status <sup>b)</sup>	1.11 (0.60–2.05)	1.09 (0.59–2.02)
Prehospital vitals		
Systolic blood pressure < 90 mmHg	14.28 (1.95–104.86)	15.89 (2.16–117.07)
Body temperature > 38°C	0.87 (0.38–2.00)	0.86 (0.37–1.96)
Blood glucose test check (yes)	0.58 (0.33–1.04)	0.57 (0.32–1.02)
Prehospital provider level	0.84 (0.55–1.31)	0.85 (0.55–1.31)

CI, confidence interval; EMS, emergency medical services.

<sup>a)</sup>Adjusted for age and sex. <sup>b)</sup>Alert versus nonalert.

group (who underwent the CPSS), 552 (23.5%) were positive for one of the three CPSS items (presence of facial palsy, asymmetric arm weakness, and speech abnormalities) in the first scenario (conservative approach). The overall diagnostic performance statistics for the EMS-assessed stroke cases were as follows: 79.5% sensitivity (95% confidence interval [CI], 75.5%–83.1%), 90.2% specificity (95% CI, 88.8%–91.6%), and 0.849 AUC (95% CI, 0.829–0.868).

Among the 2,836 participants in the second (real-world approach) and third (contrapositive approach) scenarios, 1,038 (36.6%) and 552 participants (19.5%), respectively, were deemed to be positive EMS-assessed stroke cases. The sensitivity and specificity of EMS-assessed stroke cases were 83.3% (95% CI, 80.0%–86.3%) and 75.2% (95% CI, 73.3%–76.9%), respectively, in the second scenario and 64.6% (95% CI, 60.5%–68.5%) and 91.9% (95% CI, 90.7%–93.0%), respectively, in the third scenario. No significant difference was evident in the AUC between the second and third scenarios (0.792 [95% CI, 0.775–0.810] vs. 0.782 [95% CI, 0.762–0.803],  $P > 0.05$ ).

### Prehospital factors associated with false-positive results for acute stroke in the uncooperative group

The prehospital factors that were associated with false-positive results for acute stroke in the uncooperative group are summarized in Table 3. Multivariate logistic regression revealed that seizure at EMS arrival (adjusted odds ratio [aOR], 3.27; 95% CI, 1.13–9.44), malignancy as a comorbidity (aOR, 4.36; 95% CI, 1.31–14.50), clear onset of FAT (aOR, 2.33; 95% CI, 1.50–3.61), and systolic blood pressure (SBP) < 90 mmHg (aOR, 15.89; 95% CI, 2.16–117.07) were significantly associated with increased false-positive results for acute stroke after adjustment for age and sex. In contrast, weak-

**Table 4.** Alternative clinical diagnoses (based on the final hospital ICD diagnosis code) for nonstroke patients (false positive) in the uncooperative group

Alternative diagnoses of nonstroke (false positive) patients in the uncooperative group	Value (n = 378)
Symptoms and signs (not elsewhere classified)	85 (22.5)
Convulsions (not elsewhere classified, R56)	47 (12.4)
Shock (not elsewhere classified, R58)	25 (6.6)
Syncope and collapse (R55)	13 (3.4)
Infectious diseases of a particular system	66 (17.5)
URI, influenza, and pneumonia (J00–J06, J09–J18)	31 (8.2)
Acute pyelonephritis and urinary tract infection (N10, N39)	16 (4.2)
Other sepsis (A41)	12 (3.2)
Bacterial meningitis and encephalitis (G00, G04)	4 (1.1)
Infectious gastroenteritis and colitis (A09)	2 (0.5)
Other local infections of skin and subcutaneous tissue (L08)	1 (0.3)
Mental and behavioral disorders	52 (13.8)
Dementia, delirium, and other mental disorders (F01–F09)	29 (7.7)
Alcohol, sedative, hypnotic, or anxiolytic-related disorders (F10–F19)	18 (4.8)
Mood disorders and nonpsychotic mental disorders (F30–F48)	5 (1.3)
Diabetes mellitus and metabolic complications (E10–E13)	35 (9.3)
Diabetes mellitus with hypoglycemia	27 (7.1)
Hyperglycemic-related metabolic complications	8 (2.1)
Injury, poisoning, and other effects of external causes	31 (8.2)
Injuries to the head (S00–S09)	16 (4.2)
Poisoning and toxic effects of substances (T36–T65)	11 (2.9)
Heat-related conditions (T67–T69)	4 (1.1)
Episodic and paroxysmal disorders of the nervous systems	27 (7.1)
Epilepsy and recurrent seizures (G40)	13 (3.4)
Transient cerebral ischemic attacks and related syndromes (G45)	12 (3.2)
Migraine and other headache syndromes (G43, G44)	2 (0.5)
Diseases of the liver and biliary tract	26 (6.9)
Diseases of liver (K70–K77)	23 (6.1)
Other diseases of the biliary tract (K83)	3 (0.8)
Malignant neoplasms	20 (5.3)
Malignant neoplasms of particular systems (C00–C72)	16 (4.2)
Secondary malignant neoplasms (C76–C80)	4 (1.1)
Acute kidney failure and chronic kidney disease (N17–N19)	15 (4.0)
Diseases of the circulatory system	11 (2.9)
Cardiac arrest and dysrhythmia (I44–I49)	5 (1.3)
Heart failure (I50)	3 (0.8)
Aortic aneurysm and dissection (I71)	2 (0.5)
Acute myocardial infarction (I21)	1 (0.3)
Respiratory noninfectious diseases	10 (2.6)
Chronic lower respiratory diseases (J40–J47)	5 (1.3)
Other diseases of the pleura (J90–J94)	5 (1.3)

Values are presented as number (%).

ICD, International Classification of Disease; URI, upper respiratory infection.

ness of the upper extremities (aOR, 0.10; 95% CI, 0.02–0.49) upon EMS arrival was associated with decreased false-positive instances. The remaining demographic and clinical factors were not significantly associated with false-positive results for acute stroke.

## Alternative diagnoses for nonstroke patients in the uncooperative group

Of the 486 EMS-transferred uncooperative prehospital patients suspected to have acute stroke, 378 (77.8%) were identified as false positives. The alternative diagnoses, which were classified clinically using the final hospital ICD diagnosis codes, are summarized in Table 4. The commonly documented main categories of alternative diagnoses for the false-positive patients were non-diagnosis-classified symptoms and signs (n = 85, 22.5%); infectious diseases of a particular system (n = 66, 17.5%); mental and behavioral disorders (n = 52, 13.8%); diabetes mellitus and metabolic complications (n = 35, 9.3%); injury, poisoning, and other effects of external causes (n = 31, 8.2%); episodic and paroxysmal disorders of the nervous system (n = 27, 7.1%); diseases of the liver and biliary tract (n = 26, 6.9%); malignant neoplasms (n = 20, 5.3%); acute and chronic kidney failure (n = 15, 4.0%); diseases of the circulatory system (n = 11, 2.9%); and respiratory noninfectious diseases (n = 10, 2.6%). The five most common alternative diagnoses were convulsions (n = 47, 12.4%); infectious diseases of the respiratory system, including upper respiratory infection, influenza, and pneumonia (n = 31, 8.2%); dementia, delirium, and other mental disorders (n = 29, 7.7%); diabetes mellitus with hypoglycemia (n = 27, 7.1%); and nonclassified shock (n = 25, 6.6%).

## DISCUSSION

Patients suspected of acute stroke can be medically unstable and uncooperative, and early stroke recognition in such patients is challenging in the prehospital setting [20,21]. However, little is known about prehospital evaluation of uncooperative patients suspected of acute stroke. Furthermore, the real-world performance of the current Korean EMS stroke screening policy for uncooperative prehospital patients suspected of acute stroke remains unclear. Therefore, we performed this study to clarify the final hospital diagnoses and scenario-based real-world performance of the current Korean EMS stroke screening policy for uncooperative prehospital patients suspected of acute stroke.

Although the EMS transports up to 70% of stroke patients, the proportion of uncooperative stroke patients is not well established [7,8]. In the present study, 17.1% of the patients in the uncooperative group met the prehospital criteria for suspected acute stroke. Although our data do not specify the exact proportion of uncooperative patients, previous studies have shown that 8% to 25% of stroke patients have altered mental status, which is similar to our result [22]. We found several significant intergroup differences in baseline demographic and clinical characteristics, including patient age, chief complaint at EMS arrival, FAT, activity

at onset, presence of blood glucose testing, and ED disposition. In particular, inspection of the chief complaint at EMS arrival revealed that altered mental status (78.0%) was the most common presentation in the uncooperative group, followed by seizures (10.3%) and loss of consciousness (3.7%). In a study that investigated patient characteristics that affect prehospital identification of stroke by the EMS, altered mental status was associated with a 6.5-fold higher risk that EMS providers would miss a diagnosis of stroke because the PHSST could not be performed in those patients. However, no intergroup difference was observed in our data with regard to the prevalence of a final diagnosis of ischemic or hemorrhagic stroke. These findings suggest that the number of stroke patients in the uncooperative group cannot be ignored, and that a novel stroke screening approach is needed to replace the current conventional stroke screening methods [20,22–24].

We also evaluated the real-world performance of the current Korean EMS stroke screening policy using different scenarios for uncooperative prehospital patients suspected of acute stroke. EMS providers in Korea use the CPSS as the primary PHSST for stroke identification. A recent systematic study evaluated the diagnostic performance of clinical tools for stroke identification and reported that the CPSS distinguished between acute stroke and stroke mimics with 83% sensitivity, 69% specificity, 50% PPV, and 91% NPV [15,16]. In our results of CPSS diagnostic performance in the first scenario (conservative approach), its sensitivity was 79.5% (95% CI, 75.5%–83.1%), which was in the same range as in a previous review, whereas its 90.2% specificity (95% CI, 88.8%–91.6%) and 99.3% NPV (95% CI, 99.2%–99.4%) in our study were higher than those reported in previous reviews. On the other hand, the 20.1% PPV (95% CI, 17.9%–22.6%) was less than half of that reported previously. It is plausible that these results could be related to selection of the study samples. Unlike other studies, which included only cooperative patients from a convenience sample drawn from prehospital patients subjectively suspected of acute stroke by EMS providers, our study population was systematically recruited in accordance with the national EMS stroke protocol, which is based on structured chief complaint codes and mandatory standardized records [21–29]. Therefore, our study population is inclusive and consistent irrespective of the subjective suspicions of EMS providers.

Compared with the first scenario (conservative approach), the sensitivity increased slightly, and the specificity decreased markedly in the second scenario (real-world approach). In contrast, the sensitivity decreased, and the specificity increased slightly in the third scenario (contrapositive approach). In a population with a 3% prevalence of stroke, overcalls (false positives) are expected to increase by 16,199 persons, whereas missed strokes (false neg-

atives) would decrease by 516 persons per 100,000 population in the second scenario compared with the third scenario (Supplementary Table 1) [3]. These findings provide quantitative evidence for predicting the overestimation (false positive) and underestimation (false negative) effects of changing the EMS stroke screening policy for uncooperative patients. Therefore, although there is currently no consensus on optimizing the prehospital stroke assessment policy for uncooperative patients, it is necessary to compare the EMS burden of policy options based on likely overestimation or underestimation.

Most of the currently available prehospital screening tools are designed to assess the most common symptoms of acute stroke [15,16,30]. Therefore, they all provide prehospital responders a good ability to recognize positive acute stroke cases; however, their ability to exclude stroke mimics is not good and offers only modest diagnostic accuracy [16]. Therefore, this pattern of prehospital diagnosis might lead to overestimation of acute stroke and could overburden special EMS facilities.

The diagnostic performance for distinguishing between acute stroke and stroke mimics is crucial for uncooperative patients because it is very difficult to evaluate most of the prehospital screening items in this population. This situation emphasizes the need for an alternative approach to exclude stroke-mimicking conditions in uncooperative patients. One scoring system (FABS) was developed to identify stroke mimics in patients with suspected acute stroke [16,31,32]. This scoring system is calculated based on six variables, with one point for each variable present (absence of facial droop, negative history of atrial fibrillation, age < 50 years, systolic blood pressure < 150 mmHg at presentation, history of seizures, and isolated sensory symptoms without weakness at presentation). A FABS score of  $\geq 3$  demonstrated the best overall diagnostic performance, with 90% sensitivity (95% CI, 86%–93%), 91% specificity (95% CI, 88%–93%), 87% PPV (95% CI, 83%–91%), and 93% NPV (95% CI, 90%–95%) [31].

Similar to the characteristics of the FABS scoring system, our study identified five prehospital factors that were associated with stroke mimics in the uncooperative group. Seizure at presentation, medical history of malignancy, clear onset of FAT, SBP < 90 mmHg, and absence of motor weakness of the upper extremities were significantly associated with stroke mimics in our logistic regression model after adjustment for age and sex.

Furthermore, we summarized the alternative diagnoses and the five most common stroke mimics in the uncooperative group. Together, our findings provide important insights into the potential parameters needed to facilitate triage of uncooperative patients suspected of acute stroke in the prehospital setting and the ED.

Novel advanced technologies could be another option for opti-

mal prehospital stroke triage, even in uncooperative patients [33–35]. In 2019, a systematic literature review outlined the potential of noninvasive sensor technology for prehospital stroke diagnosis and provided information on 10 noninvasive external sensor devices based on seven technologies (accelerometers, electroencephalography, microwaves, near-infrared, radiofrequency, transcranial Doppler ultrasound, and volumetric impedance phase-shift spectroscopy) [33]. However, further studies are required to verify the feasibility and validation of those prehospital stroke screening systems.

Several limitations of our study should be considered when interpreting the results. First, the principal limitation of our study is the difference in design of the study sample from previous studies, which we chose to minimize the subjective suspicions of EMS providers; in our sample, all participants who matched the chief complaint codes for prehospital patients suspected of acute stroke were used as denominators. Thus, our diagnostic performance, especially PPV, could differ from that of other studies. Second, the EMS transport-to-hospital data linkage verification was limited, and 174 EMS-transported records were not linked to hospital data. The overall match rate for unique one to one EMS transport-to-ED visits was approximately 95%. Third, our retrospective study used the ICD-10 diagnostic codes from the EMR to establish a final diagnosis, which was affected by the completeness and accuracy of the EMR. Fourth, the study population was obtained from a small subset of EMS operations in only one province, limiting the generalizability of these results to other regions.

In conclusion, the final diagnosis of acute stroke in the uncooperative group did not differ significantly from that in the cooperative group. Given the changes in overestimation (false positive) and underestimation (false negative) according to the EMS stroke screening policy for the uncooperative group, further research is needed to develop a novel stroke screening approach that is customized for evaluation of uncooperative patients suspected of acute stroke.

## SUPPLEMENTARY MATERIALS

**Supplementary Table 1.** Overestimation or underestimation effects of the emergency medical services stroke screening policy for the uncooperative group

Supplementary materials are available at <https://doi.org/10.15441/ceem.22.372>.

## ETHICS STATEMENTS

This study was approved by the Institutional Review Board of Jeju

National University Hospital (No. 2021-07-013). Informed consent was waived due to the retrospective nature of the study.

## CONFLICT OF INTEREST

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

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None.

## AUTHOR CONTRIBUTIONS

Conceptualization: SWS, WJK; Data curation: SWS, CHK; Formal analysis: SWS, JHK; Investigation: HH, CBP, JHB; Methodology: SWS, JHK, , SHL; Supervision: SWS, YJK, CHK; Validation: JHB, SKL, SYK; Visualization: SWS, CBP; Writing—original draft: SH, HH; Writing—review & editing: WJK, JHK, SKL, SYK, SHL. All authors read and approved the final manuscript.

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**Supplementary Table 1.** Overestimation or underestimation effects of the emergency medical services stroke screening policy for the uncooperative group

100,000 Population (stroke prevalence, 3%)	Scenario 2 (real-world approach)			Scenario 3 (contrapositive approach)		
	Positive	Negative	Total	Positive	Negative	Total
Stroke	2,499	501	3,000	1,983	1,017	3,000
Stroke mimic	24,056	72,944	97,000	7,857	89,143	97,000
Total	26,555	73,445	100,000	9,840	90,160	100,000

# Utilization of point-of-care ultrasound among graduates of a 4-year longitudinal medical school ultrasound curriculum

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**Objective** In 2011, School of Medicine, University of California, Irvine was among the first schools to implement a 4-year ultrasound curriculum. We aimed to find the point-of-care ultrasound (POCUS) utilization pattern among University of California, Irvine alumni.

**Methods** We surveyed University of California, Irvine alumni from the class of 2011 and beyond. Survey questions included POCUS reliance, frequency of use, and comfort with image acquisition and interpretation compared with peers. The primary outcomes were self-reported comfort and reliance on POCUS.

**Results** We received 93 responses from 624 surveyed alumni (response rate, 14.9%), of which 87 were analyzed. Although 46 respondents (52.9%) reported more reliance on POCUS, three (3.4%) relied on it less than their peers. At the same time, 72 (82.7%) and 67 (77.0%) felt more comfortable than their colleagues in obtaining and interpreting POCUS, respectively. No respondents felt less comfortable obtaining or interpreting POCUS than their peers. The frequency of POCUS use correlated directly with the frequency with which POCUS changed the responder's case management ( $\rho$ , 0.860;  $P < 0.001$ ). POCUS reliance also correlated with respondents' comfort level in obtaining ( $\rho$ , 0.321;  $P < 0.001$ ) and interpreting ( $\rho$ , 0.378;  $P < 0.001$ ) POCUS results.

**Conclusion** University of California, Irvine graduates had higher reliance on POCUS than peers in their respective specialties. Their POCUS findings frequently changed their case management.

**Keywords** Diagnostic ultrasound; Point-of-care ultrasound; Ultrasound curriculum; Emergency medicine

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## Capsule Summary

### What is already known

*During the past decade, point-of-care ultrasound has become increasingly common across most medical specialties, and its use as an educational tool has risen in medical schools.*

### What is new in the current study

*Graduates of a 4-year medical school ultrasound curriculum have higher reliance and comfort with point-of-care ultrasound relative to peers in their respective specialties, indicating that familiarity and experience with ultrasound before reaching postgraduate training makes students conversant in an increasingly valuable skill.*

## INTRODUCTION

Ultrasound was first used as a medical diagnostic tool in the 1930s, and its applications have expanded into 20 medical specialties in the past decade [1–3]. During the past several years, ultrasound technology has advanced, allowing for better resolution and portability and spurring the birth of point-of-care ultrasound (POCUS), which is performed and interpreted in real-time by physicians [3]. This rapidly expanding field has revolutionized medicine by allowing physicians to obtain and interpret images at the bedside, complementing the physical exam and facilitating early diagnosis [3–5]. As the first line of diagnostic imaging worldwide, POCUS has become widely used in most specialties [4]. As ultrasound becomes more prevalent among specialties, residency program requirements are beginning to reflect this clinical change [4,5]. For specialties such as emergency medicine, obstetrics and gynecology (OBGYN), ophthalmology, physical medicine and rehabilitation (PM&R), psychiatry, neurology, radiology, and urology, the Accreditation Council for Graduate Medical Education (ACGME) now requires competency in ultrasound [4–6].

Despite the known benefits of bedside ultrasound in a patient evaluation, the utility of providing ultrasound education for faculty and residents remains a contentious issue within many specialties [5,6]. The increased use of POCUS in different fields and insufficient training warrant a standardized guideline for ultrasound in medical education. This ongoing paradigm shift in imaging and clinical practice has encouraged medical schools nationally to implement a fully integrated ultrasound curriculum [7–11]. Early exposure to ultrasound throughout undergraduate medical education not only augments student understanding of anatomy and physiology through real-life application, but also increases their comfort and competence with the technology [12–14].

The class of 2011 was the first class to have a longitudinal ultrasound curriculum at the University of California, Irvine. The goal of this study was to explore those alumni's use, comfort, and

reliance on ultrasound in their current specialty a few years after graduation.

## METHODS

University of California, Irvine was one of the first medical schools to implement a 4-year longitudinal ultrasound curriculum. Students watch a minimum of two 30-minute web-based lectures before every session to supplement their preclinical schedule [14]. The 1st year consists of eight hands-on 1-hour sessions and a practical exam to assess student skill levels. A 1:4 ratio of 4th-year medical student instructors to students is maintained for each session, and a simplified list is given to each student at the beginning of class to ensure that all competencies are met [14]. Second-year students receive an additional 11 hours of hands-on ultrasound practice and have an objective structured clinical examination (OSCE) evaluation at the end of the year. By the end of their 2nd year, students are competent in obtaining ultrasounds and identifying pathology in the following systems: cardiovascular, gastrointestinal, genitourinary, respiratory, musculoskeletal, and head and neck. Ultrasound is implemented in 3rd- and 4th-year rotations and OSCEs. An additional 3rd- and 4th-year ultrasound clerkship is offered to students, and it requires a minimum of 75 scans/wk, quality assurance meetings, and participation in Ultrasound Journal Club [14].

We emailed an online voluntary survey to 624 alumni with a graduation date starting in 2011, the first graduating year after the longitudinal ultrasound curriculum was introduced. With 93 responses, we had a response rate of 14.9%. We collected the following data: year of graduation, specialty, reliance on POCUS in practice, frequency of POCUS utilization, and comfort with POCUS image acquisition and interpretation. According to our Institutional Review Board (IRB) guidelines, this study qualified for IRB exemption because no identifying information was collected. There was no risk or minimal risk to subjects for participating in

this survey.

We used the Pearson chi-square test to determine differences between categorical variables and Spearman's rho correlation coefficient to examine associations between ordinal variables. We used the one-sample Kolmogorov-Smirnov test to examine the distribution of the answers and analyzed all data using IBM SPSS ver. 26.0. (IBM Corp).

## RESULTS

Ninety-three responders completed the survey (Table 1). Answers from six psychiatrists were excluded because POCUS has little application in this specialty. Emergency medicine ( $n = 24$ , 27.6%), OBGYN ( $n = 9$ , 10.3%), family medicine ( $n = 8$ , 9.2%), pediatrics ( $n = 7$ , 8.0%), and anesthesiology ( $n = 6$ , 6.9%) were the most fre-

**Table 1.** Survey questions and distribution of responders' answers ( $n=93$ )

Question and answer	No. (%)
What year did you graduate from School of Medicine, University of California, Irvine?	
2011	1 (1.1)
2013	1 (1.1)
2014	12 (12.9)
2015	7 (7.5)
2016	16 (17.2)
2017	21 (22.6)
2018	14 (15.1)
2019	21 (22.6)
What is the most common POCUS you use? <sup>a)</sup>	
Procedural guidance	48 (12.9)
Cardiac	46 (12.3)
Lung	41 (11.0)
Trauma/FAST	38 (10.2)
Obstetric/gynecologic	34 (9.1)
Renal	32 (8.6)
Biliary	30 (8.0)
Vascular	29 (7.8)
Musculoskeletal/soft tissue	27 (7.2)
Ocular	27 (7.2)
Other	21 (5.6)
How many times did POCUS change your management during the past 3 months? ( $n = 92$ ) <sup>b)</sup>	
0	22 (23.9)
1–3	29 (31.5)
4–6	12 (13)
7–9	5 (5.4)
10–12	2 (2.2)
> 12	22 (23.9)

POCUS, point-of-care ultrasound; FAST, focused assessment with sonography for trauma.

<sup>a)</sup>The sum exceeds the sample size as responders were allowed to report as many POCUS as they wish. <sup>b)</sup>One missing data.

quent specialties among the responders. The most frequent POCUS users were practicing in cardiology, pulmonology and critical care, PM&R, emergency medicine, and OBGYN (Fig. 1).

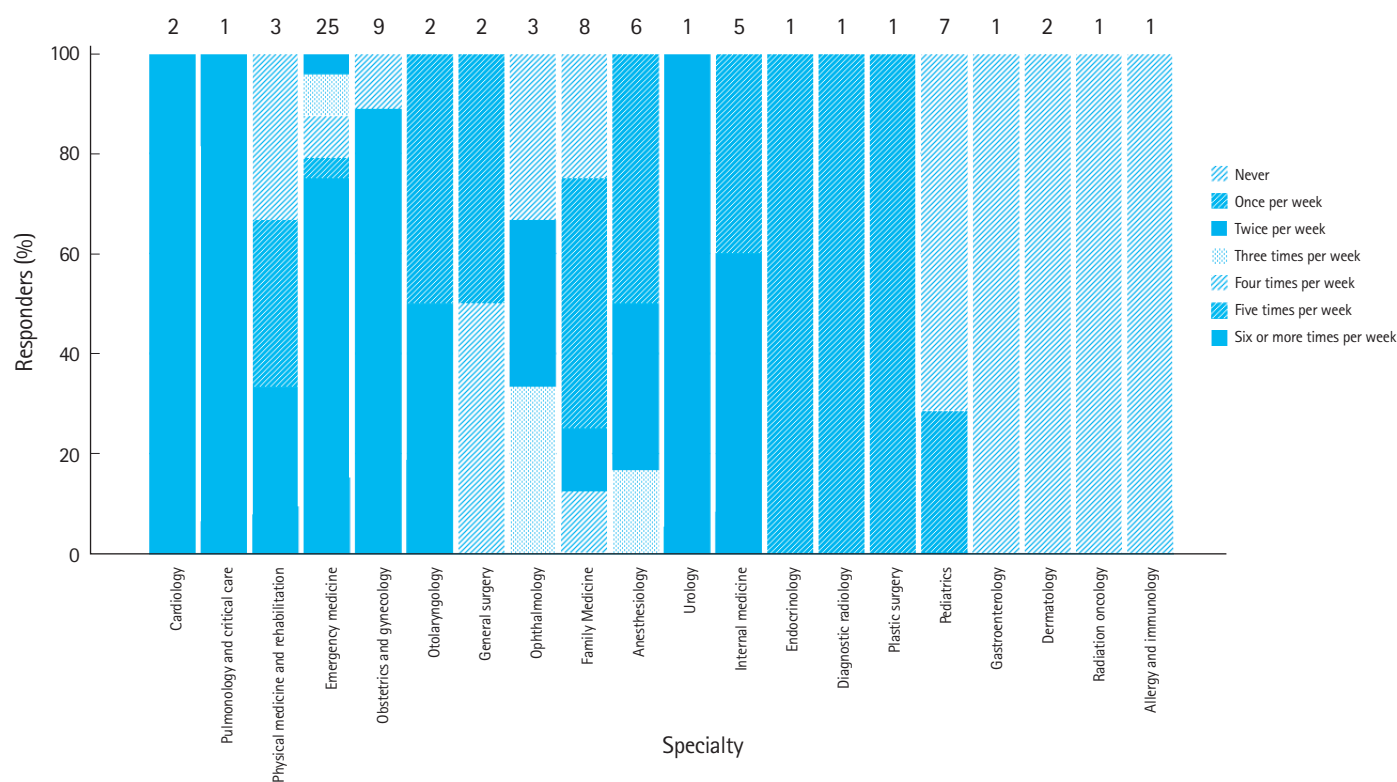
POCUS changed the practice of 70 responders (80.5%) at least once in the 3 months prior to the survey. The practice of responders from emergency medicine changed more frequently than that of other respondents as a result of POCUS exams ( $P < 0.001$ ). The frequency of POCUS changing the responder's practice during the past three months correlated directly with the frequency of POCUS use ( $\rho$ , 0.860;  $P < 0.001$ ).

Fig. 2 shows the reliance of responders on POCUS and their perceived comfort in obtaining and interpreting POCUS, compared with their peers in their current specialty. The distribution of answers showed a shift to the right and was not symmetrical ( $P < 0.001$ ). Although 46 responders (52.9%) found their reliance on POCUS to be more or much more than their peers, three (3.4%) relied less or much less on POCUS than peers in their specialty. At the same time, 72 (82.7%) and 67 (77.0%) felt more or much more comfortable than their peers with obtaining and interpreting POCUS, respectively. None of the responders felt less comfortable obtaining or interpreting POCUS than their peers in their current specialty. Reliance on POCUS correlated with the comfort level of the responder in obtaining ( $\rho$ , 0.321;  $P < 0.001$ ) and interpreting ( $\rho$ , 0.378,  $P < 0.001$ ) POCUS results.

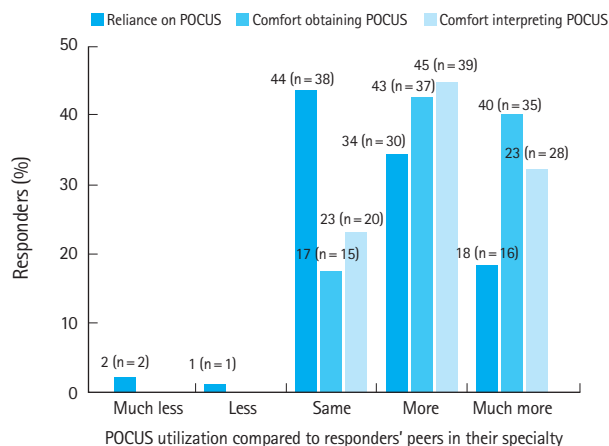
## DISCUSSION

The results of our study show that University of California, Irvine graduates who underwent a longitudinal 4-year ultrasound curriculum reported higher comfort levels in obtaining and interpreting POCUS than their peers. This comparison was made by the participants themselves in relation to colleagues within their specialty. We also found that reliance on ultrasound correlated with the respondents' comfort in obtaining and interpreting POCUS results. More than half of our respondents relied on POCUS and felt more comfortable obtaining and interpreting POCUS results than peers in their field. Very few, if any, were less reliant or comfortable than their peers. This suggests that a 4-year longitudinal ultrasound education during medical school would improve reliance on and use of POCUS in residency and beyond.

The number of times POCUS is used per week was heavily affected by what specialty the graduates went on to practice in, with cardiology, pulmonology and critical care, PM&R, and emergency medicine being the highest users of POCUS. These findings are not surprising because these specialties have many more validated applications for POCUS than the specialties lower on the list. We therefore asked respondents to assess their reliance and



**Fig. 1.** Percentage of responders by specialty in point-of-care ultrasound (POCUS) utilization patterns. The numbers represent the number of responders (n=82, one missing data).



**Fig. 2.** Percentage of responders' reliance on point-of-care ultrasound (POCUS) and perceived comfort obtaining and interpreting POCUS, compared with peers in the same specialty.

comfort with POCUS in comparison to peers in their field as a control for the overall differences in baseline POCUS use between specialties. Applications for ultrasound continue to grow each year across most fields of medicine, making familiarity and experience with ultrasound prior to postgraduate training an increasingly valuable skill [15–17]. Additionally, with ultrasound technology continuing to become more portable and affordable, it is

expected that POCUS utilization will continue to rise [5,18–20].

A limitation of this study is that our data are inherently subjective because we asked respondents to assess their own reliance and comfort with POCUS relative to their peers. The respondents might vary in their self-awareness and judgment of ability and thus in their ability to accurately compare their own comfort and skill with that of their peers. In short, our data are open to several cognitive biases. One way to address this potential bias could be to include a control group by sending the same survey to physicians who graduated from a medical school without a 4-year ultrasound curriculum and looking for a statistically significant difference in reported comfort with POCUS between the groups. A potential follow-up study could aim to re-create these findings with objective data such as the number of POCUS scans logged or proficiency at POCUS on clinical milestones. This could be feasible if the scope of the study were scaled down to just one specialty, such as emergency medicine, in which it is common practice for residency programs to track the number of POCUS scans performed and include POCUS as part of the assessment for clinical competency.

In conclusion, this study shows that graduates of a 4-year longitudinal medical school ultrasound curriculum reported that they subjectively had higher reliance and comfort with POCUS than their peers in their respective specialties. POCUS is undoubt-

edly becoming more accessible and widely used across many if not all specialties, which supports the value of incorporating ultrasound into the medical school curriculum.

## SUPPLEMENTARY MATERIALS

**Supplementary Material 1.** Course description.

Supplementary material is available from <https://doi.org/10.15441/ceem.22.357>.

## ETHICS STATEMENTS

Not applicable.

## CONFLICT OF INTEREST

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# The usual sedative dose in very elderly patients with a good neurological outcome after cardiac arrest can cause a suppressed background and burst suppression: two case reports

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Highly malignant electroencephalogram (EEG) patterns (including suppressed background and burst suppression) refer to a poor neurological outcome in cardiac arrest patients, but some of those patients may show a good neurological outcome. This is the first report that details the reason for their uncommon survival despite highly malignant EEG patterns after cardiac arrest. The brain cortical activities in very elderly patients (who are vulnerable to the usual sedative doses) showed a suppressed background and burst suppression but resulting in a good neurological outcome. The mean suppression rates from their EEGs were 100% and 68.4%, respectively, and a normal pattern was completely restored after the sedatives had affected their brain waves for 12 hours. It was speculated that sedatives given at an ordinary dose may negatively affect the brain's cortical activity in elderly patients who demonstrate a good neurological outcome. When appropriate doses of sedatives are used, highly malignant EEG patterns in very elderly patients should be carefully interpreted for early neuroprognostication.

**Keywords** Heart arrest; Electroencephalography; Hypnotics and sedatives; Brain hypoxia; Case reports

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## Capsule Summary

### What is already known

Highly malignant electroencephalogram patterns indicate a poor neurological outcome in cardiac arrest patients. However, several studies have reported that patients with these patterns can show a good neurological outcome, although the reasons are obscure.

### What is new in the current study

The mean suppression rate based on electroencephalogram results in very elderly patients may be increased because the usual sedative dose may affect their brain's cortical activity. Highly malignant electroencephalogram patterns in very elderly patients may be misinterpreted for early neuroprognostication and may in fact not lead to such grave outcomes.

## INTRODUCTION

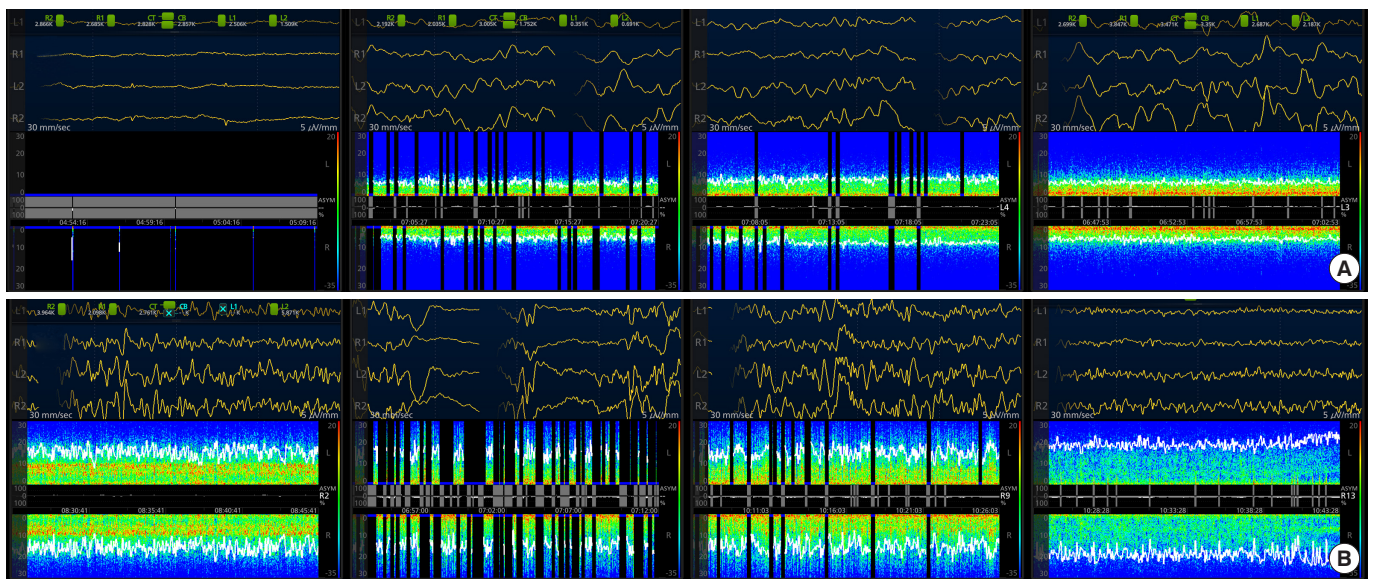
There have been concerns about early neuroprognostication in cardiac arrest patients with highly malignant electroencephalogram (EEG) patterns because several patients have experienced good neurological outcomes despite a suppressed background or burst suppression 12 hours after hospital admission [1–3]. However, others have reported that highly malignant EEG patterns can predict neurologic outcomes at an early stage [4]. It is well known that EEGs are affected by sedative doses, but EEG suppression due to an appropriate use of sedatives in cardiac arrest patients is not sufficient to change the neurological outcomes [3,5]. To observe the change in the mean suppression rate (MSR) from the EEGs of patients with malignant and highly malignant EEG patterns, cardiac arrest patients in our hospital were monitored with frontal EEGs, which can automatically measure suppression ( $<10 \mu\text{V}$ ) in an EEG background. We have found that two patients who did regain alertness were elderly, and frontal EEG monitoring showed a suppressed background and burst suppression. They were predicted to experience a poor neurological outcome. Similar episodes did not occur in our hospital in younger patients or even in most elderly patients when appropriate doses of sedatives were used; therefore, we report a severe increase in MSR caused by the appropriate augmentation of sedative doses.

## CASE REPORTS

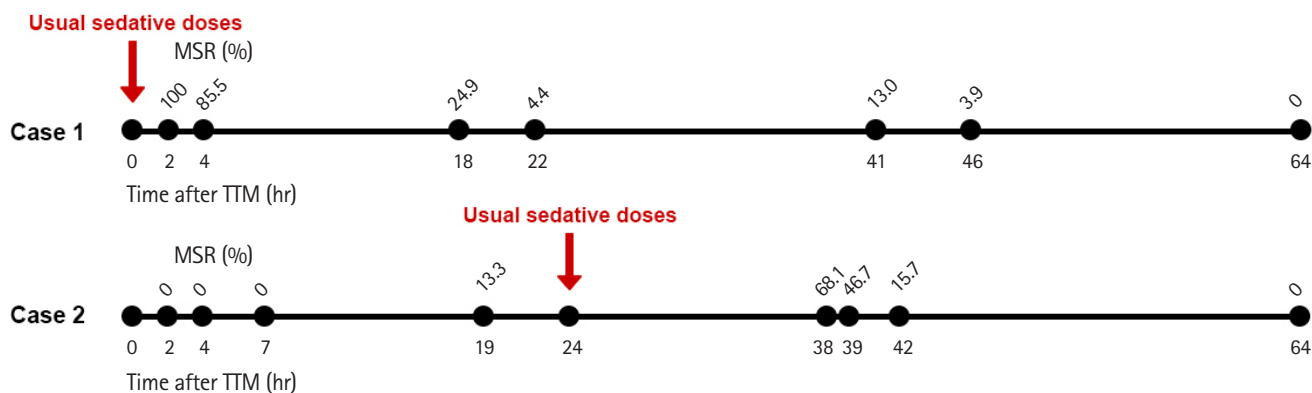
### A case with suppressed background and a good neurological outcome

An 80-year-old male patient who had a history of unstable angina, hypertension, diabetes mellitus, and stage 3 chronic kidney disease was found on the street by a bystander. The bystander performed cardiopulmonary resuscitation (CPR) for 6 minutes after he immediately called the emergency services. When an ambulance arrived 6 minutes after the emergency phone call, an emergency medical technician performed CPR for 6 more minutes with two defibrillations. A return of spontaneous circulation (ROSC) was achieved. Upon arrival at the hospital, the patient was hypotensive with a blood pressure of 70/50 mmHg; pulmonary edema and cardiomegaly were visible on a chest X-ray. Initially, he exhibited stupor with a reactive pupillary reflex. Targeted temperature management (TTM) was induced with a surface-cooling device and sedation was initiated according to our TTM protocol; the starting dosages of propofol and remifentanyl were 20 and 0.1  $\mu\text{g}/\text{kg}/\text{min}$ , respectively, but the dosages were increased upon re-evaluation as sedation was inappropriate due to the patient's movement.

Sedatives were started; the dosage (propofol 50  $\mu\text{g}/\text{kg}/\text{min}$  and remifentanyl 0.2  $\mu\text{g}/\text{kg}/\text{min}$ ) was higher than an ordinary starting



**Fig. 1.** Frontal electroencephalograms (EEGs) in patients with a suppressed background and burst suppression. (A) A suppressed background 2 hours after targeted temperature management (TTM), a discontinuous background 18 hours after TTM, a discontinuous background 41 hours after TTM, and a continuous background 64 hours after TTM from the far left. (B) A continuous background 2 hours after TTM, burst suppression 38 hours after TTM, a discontinuous background 42 hours after TTM, and a continuous background 64 hours after TTM from the far left. A color density spectral array (CSDA) was plotted with frequency and time along the Y-axis and X-axis, respectively. The upper and lower columns of the CSDA show the left and right brain waves, respectively. The amplitudes of these brain waves correspond to colors (red, yellow, green, azure, and blue) on a decibel scale. Black (or black bars) with blue bottoms at 0 Hz indicate suppressions; the mean suppression rate in the screenshot of CSDA for 20 minutes was manually calculated.



**Fig. 2.** The changes in mean suppression rate (MSR) according to time points. MSR gradually changed from 100% to 0% and from 68.1% to 0% over time after administration of usual sedative doses in cases 1 and 2, respectively. TTM, targeted temperature management.

dosage, but it was still tolerable and has been reported in other studies [6,7]. The sedatives were maintained at the same dose for 58 hours and then afterwards tapered by reducing propofol by 10  $\mu\text{g/kg/min}$  and remifentanyl by 0.2  $\mu\text{g/kg/min}$  every 4 hours. Frontal EEG monitoring was performed at the start of the TTM using a Sedline brain function monitor (Masimo Corporation, Irvine, CA, USA), which consists of four flexible electrodes placed on the forehead at Fp1, Fp2, F7, and F8. Initially, the background EEG showed a normal trace, but 2 and 4 hours after the start of sedation and TTM, the MSR rose to 85.5%–100%, and a poor neurological prognosis was predicted due to the suppressed background (Figs. 1A, 2). On day 2 (over 18 hours after the initiation of sedatives), the MSR had been reduced to 24.9% (discontinuous background) and 4.4% (Figs. 1A, 2). The MSR changed to 3.9%–13% on day 3 before tapering the sedatives, and no suppression was observed on day 4, when the sedatives were stopped 72 hours after beginning TTM.

On day 4, the mental status of the patient had improved from a semicomatose state to a deep stupor, and he began having spontaneous eye opening when asked to do so. During day 5, his consciousness gradually recovered becoming drowsy and responsive to commands. He was eventually diagnosed with cardiac arrest due to heart failure and pulmonary edema, and on day 21 after admission, he was alert and discharged in stable condition after receiving supportive care to treat the pulmonary edema, delirium, and wound infection during admission.

### A case with burst suppression and a good neurological outcome

An 83-year-old female patient suddenly collapsed in front of her place of residence. A lay rescuer witnessed her fall and performed CPR for 5 minutes. Soon after, an emergency medical technician arrived at the scene and performed CPR with one defibrillation at

10 minutes. The patient's initial heart rhythm showed pulseless electric activity, but she eventually achieved ROSC. Upon arrival at the hospital, she was stuporous, and her pupil size and reflexes were 2+/2+. Her initial blood pressure was 80/40 mmHg but improved shortly thereafter. TTM was induced with a surface-cooling device after admission, and she was given sedation according to our TTM protocol.

The starting dosage of propofol was 40  $\mu\text{g/kg/min}$ , while that of remifentanyl was 0.1  $\mu\text{g/kg/min}$ . Frontal EEG monitoring was performed at the start of the TTM. Alpha and beta waves in her frontal lobe were largely observed on day 1, but MSR on day 2 was abruptly increased from 0% to 13.3%. A physician raised the dosages of the sedatives to 50  $\mu\text{g/kg/min}$  of propofol and 0.2  $\mu\text{g/kg/min}$  remifentanyl because her patient state index was increased on day 2 and thereafter, and her EEG also showed a burst suppression, which was increased to 68.1% of MSR (38 hours after starting sedatives, 14 hours after raising the dose) (Figs. 1B, 2). Moreover, the patient developed a pinpoint pupil after increasing the remifentanyl dosage from 0.1 to 0.2  $\mu\text{g/kg/min}$ . The burst suppression was changed to a discontinuous background, and the MSR was gradually reduced to 15.7% (41 hours after starting sedatives and 18 hours after raising the dose), although the dose of the sedatives was not decreased (Figs. 1B, 2). As the doses of the sedatives were decreased over the rewarming period, her EEGs recovered with normal background activity and without any suppression on day 4. Sedatives were totally stopped at 72 hours after starting TTM.

On day 4, the patient was still in a coma, and nonreactive pinpoint pupils were noted. However, on day 5, she started waking and was responsive to commands. Small multiple lacunar infarctions were noted on her brain magnetic resonance imaging scan, but those lesions were not considered to be of much clinical significance. She was eventually diagnosed with a non-ST elevation

myocardial infarction due to an unknown cause, and on day 10 after admission, she had stable vital signs and was transferred to another hospital in an alert to drowsy mental condition.

## DISCUSSION

Physicians who treat cardiac arrest patients need to consider early neuroprognostication so they may counsel families and make management decisions to urge aggressive treatment or to avoid inappropriate treatment [8]. For accurate early neurological prognostication, it is essential to note that very elderly patients may present with a suppressed background or burst suppression, especially at the beginning of sedation, because the brains of elderly patients may be very sensitive to sedatives [9,10].

The causes that have led to considerably suppressed backgrounds during propofol–remifentanyl anesthesia in surgical patients have been previously studied [11]. Age was the most important risk factor; patients >80 years old were noted to be at highest risk with an odds ratio of 10.59, while patients who were 60 to 80 years old had an odds ratio of 4.8. Our patients were 80 and 83 years old, respectively, and the increase in sensitivity to sedatives in their brain was most likely due to their advanced age. An immoderate impact on the brain after a mild opioid dose was identified in the female patient because she developed a pinpoint pupil that occurred after appropriately increasing the remifentanyl dose. This pinpoint pupil arose in conjunction with burst suppression.

The brain's susceptibility to sedatives in elderly patients has never been described in studies on the neuroprognostication of cardiac arrest patients. A suppressed background and burst suppression are considered to be highly malignant EEG patterns and have rarely been observed in patients who go on to experience a good neurological outcome. Nonetheless, a study that included 240 patients reported that all patients with an isoelectric EEG ( $<2\ \mu\text{V}$ ) died, but there were several patients with a good neurological outcome who had a suppressed background (11 patients) and burst suppression (four patients) at 12 hours after a cardiac arrest [1]. The authors surmised that a suppression pattern on EEG was still compatible with neurological recovery 12 hours after ROSC, but the reason for such a phenomenon was not revealed. The patients were a mean of 60.8 years of age, and the third interquartile value was 95 years. The vulnerability of their brains to sedatives due to their advanced age might have increased the suppression pattern in these patients. Another study could not exclude the possibility that the onset of suppressed background in the patients who survived might result from an interference between the EEG and propofol, but vulnerability due

to a very old age was still disregarded [2].

The increased MSR that resulted from using routine sedative doses in elderly patients with good neurological outcomes may be persistent for 12 hours or more before gradually decreasing regardless of any tapering of the doses of sedatives; patients may still completely recover while the effects of sedatives on EEGs disappear by day 3 or 4. For early neuroprognostication upon EEG testing in patients who are quite elderly (approximately 80 years of age or older), sedatives should be started at a lower dose when possible. An early prediction of a poor neurological outcome based solely on the EEG without considering a patient's advanced age and sedative dose might lead to false prediction. In very aged patients who are restored from cardiac arrest, physicians should recognize that even ordinary sedative doses can affect the brain's cortical activities and create more suppressions.

## ETHICS STATEMENTS

The patients provided informed consents for publication of the research details and clinical images.

## CONFLICT OF INTEREST

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

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# Digital healthcare: the new frontier of holistic and efficient care

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## INTRODUCTION

The landscape of healthcare is rapidly evolving, driven by cutting-edge technological advancements that aim to improve patient outcomes, increase efficiency, and reduce costs. This commentary will discuss five points to consider in digital healthcare: healthcare in augmented reality (AR) and the metaverse, digital therapeutics, holistic healthcare, interoperability, and artificial intelligence (AI) for healthcare workers.

## HEALTHCARE IN AR AND THE METAVERSE

AR and metaverse technologies are increasingly being utilized in healthcare to address chronic pain and offer immersive experiences for patient education, training, and treatment [1]. With AR, patients can visualize their conditions, enabling them to better understand their symptoms and the effects of treatments. For instance, AR-based therapy can help chronic pain patients gain control over their pain perception and improve their quality of life [2]. The metaverse, on the other hand, provides a virtual environment where patients can undergo therapy and rehabilitation sessions, participate in support groups, and interact with healthcare providers in a more engaging and accessible way [3].

## DIGITAL THERAPEUTICS

The increasing use of smartphones, wearables, and other connected devices has resulted in a new modality of treatment—digital therapeutics [4,5]. These solutions use evidence-based software programs to deliver personalized, clinically-supported interventions to patients, often without the need for in-person consultations. One notable example is EndeavorRx (Akili Interactive Labs), a video game-based therapy for children with attention deficit hyperactivity disorder (ADHD) approved by the US Food and Drug Administration (FDA) [6]. Digital therapeutics can complement or even replace traditional treatment methods, offering new possibilities for remote care and patient monitoring [7,8].

## HOLISTIC HEALTHCARE

Holistic healthcare, or whole-person health, shifts the focus from isolated diagnosis and treatment to a comprehensive approach that encompasses the entire cycle of care [9]. Companies like Omada Health emphasize prevention, early intervention, and long-term support to help pa-

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tients manage chronic conditions more effectively [10]. This approach recognizes that health is multifaceted, and factors such as mental, emotional, and social well-being must be addressed to achieve lasting improvements. Using technology, healthcare providers can track patient progress, offer tailored interventions, and maintain ongoing communication to ensure optimal outcomes.

## INTEROPERABILITY

Interoperability is the seamless exchange of information across healthcare systems and platforms. It aims to reduce redundancy, streamline care coordination, and empower patients to make informed decisions [11]. In Korea, the government-initiated "My Healthway" project is a notable example of efforts to improve interoperability [12]. This platform consolidates patient health information and shares it with consumers and healthcare providers upon receipt of consent, leading to more personalized and efficient care. This approach mirrors the financial "MiData" service [13], which has been successful in revolutionizing the banking industry.

## AI FOR HEALTHCARE WORKERS

AI is also transforming the healthcare sector by providing valuable support to medical professionals. From automating patient surveys to generating voice-activated medical records, AI-powered tools are enhancing efficiency and reducing administrative burdens. One such success story is Nuance DAX (Nuance), which can generate accurate medical records by listening to conversations between patients and physicians [14]. Also, AI-assisted radiograph readings and other diagnostic tools are becoming more commonplace, allowing healthcare workers to make better decisions and focus on delivering high-quality care. In Korea, the Naver Corporation provides services for healthcare workers, such as Smart Survey, which facilitates previsit questionnaires and automatically records them to the electronic medical records. Also, the same company's patient summary solution reduces clinician burden by automatically suggesting appropriate messages to be sent out to patients based on results of a medical checkup.

## CONCLUSION

The era of large language models and digital innovation offers numerous possibilities for both patients and healthcare professionals [15]. By embracing new technologies, the healthcare industry can provide more effective, personalized, and holistic care, ultimately leading to improved patient outcomes and a better

overall experience for all.

## ETHICS STATEMENTS

Not applicable.

## CONFLICT OF INTEREST

Dongchul Cha works for Naver Corporation (Seongnam, Korea). No other potential conflict of interest relevant to this article was reported.

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# Hyperacute presentation of fat embolism syndrome after multiple long bone fractures

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A 69-year-old woman presented to the emergency room with right arm pain after a fall. She was alert and had no other symptoms. She had no relevant medical history. The radiograph showed a right distal radius fracture and fracture of the surgical neck of the humerus (Fig. 1). After 1 hour, she had a sudden change in consciousness, with no response to pain stimulus. Brain computed tomography (CT) was performed immediately but showed no intracranial hemorrhage. Subsequent brain magnetic resonance imaging (MRI) showed multiple embolic infarcts (Fig. 2). In addition, chest CT showed pulmonary thromboembolism (Fig. 3). A second brain MRI performed 2 days after hospitalization showed multiple embolic infarcts with progression (Fig. 4). No evidence of an embolic source was found in the electrocardiogram and echocardiography. The patient remained in a state of stupor mentality throughout the 2-month inpatient treatment. Additionally, the electroencephalogram examination confirmed the presence of epilepsy. After undergoing conservative treatment for 2 months, the patient was transferred to a rehabilitation hospital.

Although histological confirmation was not performed, sudden neurologic deficits, tachypnea, and disseminated intravascular coagulation after long bone fractures strongly suggested fat embolism syndrome (FES), a rare and fatal complication that can occur after a long bone fracture [1-3]. FES usually occurs between 12 and 72 hours postfracture and rarely occurs before 12 hours [2]. This patient developed FES 90 minutes after injury, which is very rare. Neurological symptoms or signs of cerebral FES vary widely, ranging from headache, diffuse encephalopathy, aphasia, and seizures [4,5]. FES should be considered in the differential diagnosis of patients with sudden changes in mental status immediately after a long bone fracture.

## ETHICS STATEMENTS

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

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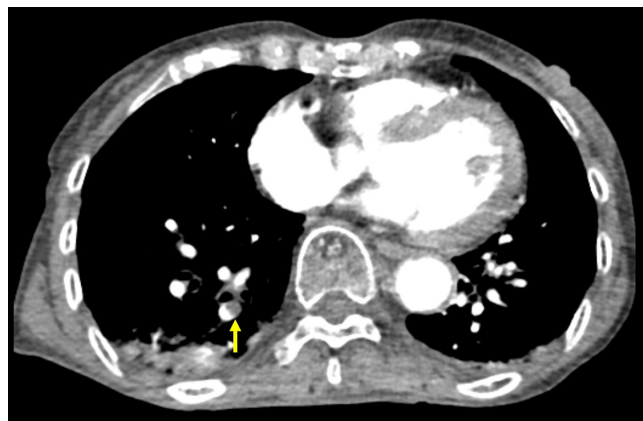
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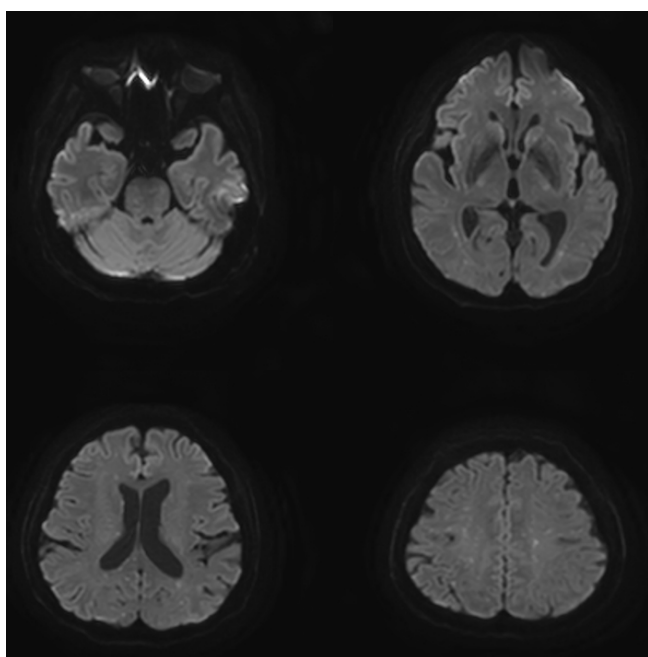
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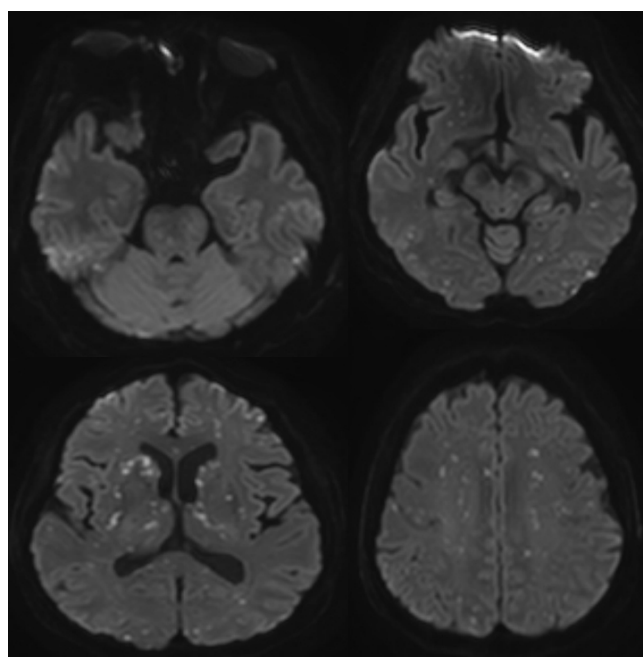
**Fig. 1.** Initial x-ray showing multiple bone fractures, including right distal radius and the surgical neck of the humerus.



**Fig. 3.** Pulmonary artery thromboembolism in sub-subsegmental pulmonary arteries in the right lower lung (arrow). The embolus site was 12 Hounsfield units.



**Fig. 2.** Magnetic resonance imaging 2 hours after injury demonstrating findings of tiny, multifocal, diffusion-restrictive lesions in both the cerebrum and cerebellum.



**Fig. 4.** Magnetic resonance imaging 2 days after injury shows an increased number of tiny, multifocal, diffusion-restrictive lesions in the cerebrum, midbrain, pons, and cerebellum.

## AUTHOR CONTRIBUTIONS

Conceptualization: SKO; Data curation: YNI, SKO; Investigation: SKO; Methodology: JHM; Resources: YNI; Software: JHM; Supervision: SKO; Validation: SKO; Visualization: YNI, SKO; Writing-original draft: JHM, SKO; Writing-review & editing: all authors. All authors read and approved the final manuscript.

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# Treatment with *Vitis vinifera* extract for controlling ascites and local swelling in snakebites

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Dear Editor,

The pit viper, which belongs to the Viperidae family, is the most common venomous snake in Northeast Asia [1]. This snake's venom does not severely affect the human body, and most victims only experience mild to severe local symptoms such as pain, swelling, and necrosis in the bite area [1,2]. Although antivenom therapy is available for fatal snakebite treatment, it offers little to no protection against local effects such as dermonecrosis, myonecrosis, edema, hemorrhage, and inflammation in the bite region [1,2]. Local symptoms can result in serious complications such as compartment syndrome and rhabdomyolysis. Swelling in the bite region is a common and major cause of serious complications for which negative pressure wound therapy has been shown effective [2–6]. However, a definitive treatment has yet to be determined.

*Vitis vinifera* seed extract (VSe) has been studied as an antivenom for snakebites and is useful for neutralization of various venom-induced activities [3–6]. It is reportedly effective in the treatment of bites by snakes from the Viperidae family and Russell's and hump-nosed vipers [3–6]. The local effects of viper bites can be treated with VSe through neutralization of the venom's edema-inducing and myonecrotic properties. VSe has been reported to abolish hyaluronidase and proteolytic activities, neutralizes hemorrhage, and partially inhibits procoagulant activity attributed to viper venom [3–6].

We report two cases of successful treatment of snakebites with VSe. The first patient was treated for ascites that passed through the groin to the abdomen, resulting in increased severe leg swelling following a snakebite. The second patient exhibited hypersensitivity to the antivenom.

The first case was a 15-year-old female patient with no past medical history admitted for a snakebite on the left heel. She had severe localized pain followed by swelling and bruising of the foot. The patient arrived at the emergency department of a local hospital 10 minutes following the snakebite, with progressive swelling of her left leg and ecchymosis around the fang marks. Kovax freeze-dried *Gloydius brevicaudus* antivenom 6,000 units (6,000 units/vial, Korea Vaccine) was injected intravenously immediately after arrival at the hospital. A splint was applied for immobilization. The patient reported generalized abdominal pain but no bleeding from the gums, epistaxis, hemoptysis, hematemesis, melena, vaginal bleeding, breathing difficulty, focal neurological deficit, or loss of consciousness. The swelling progressed rapidly to the knee within the

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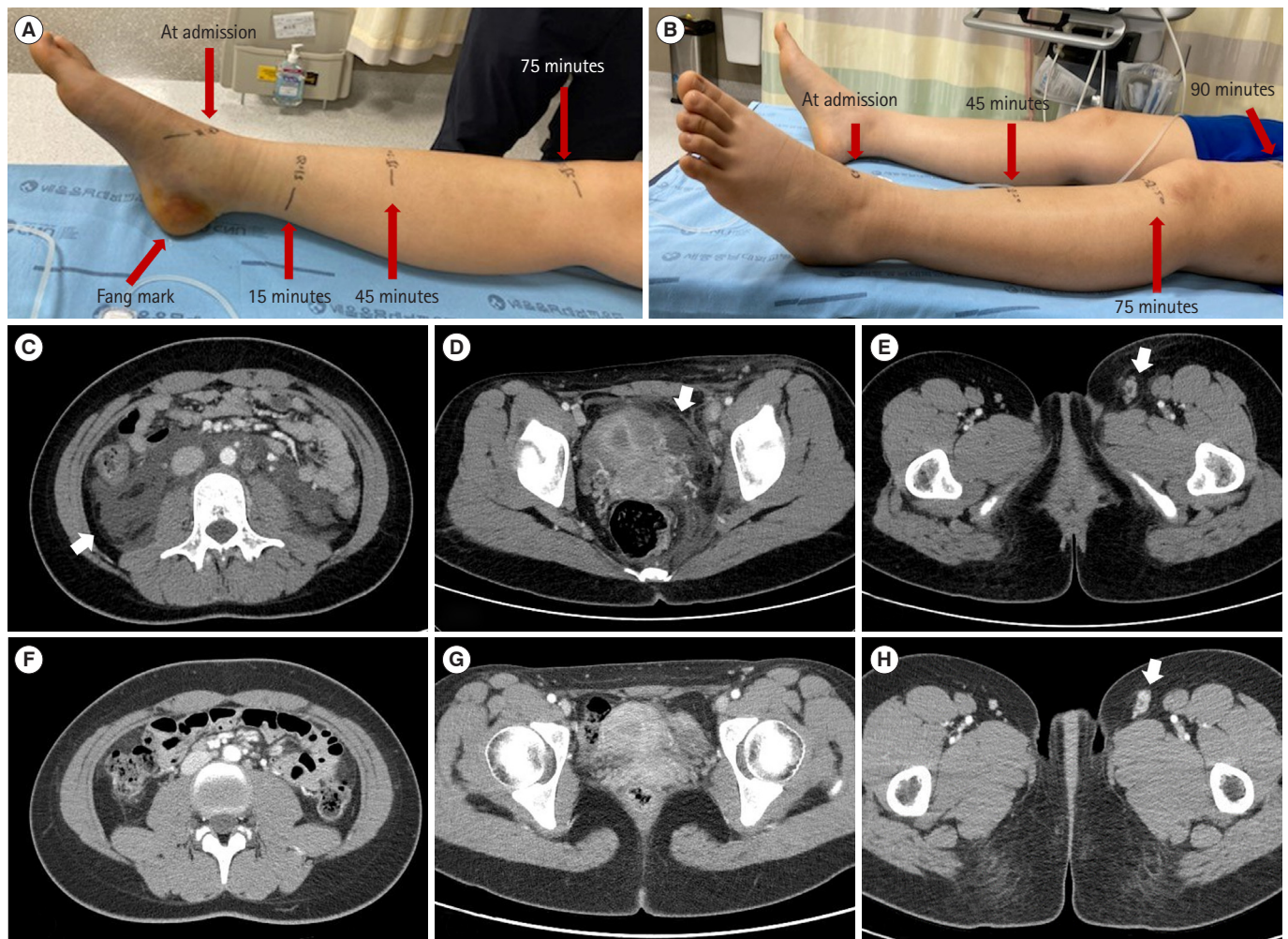
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1st hour and proximally to the hip and inguinal area within 2 hours (Fig. 1). The local effect score was 13 (pain, 4; swelling, 4; ecchymosis, 2; time, 3). In addition, the patient developed marked pain in her leg up to her lower abdomen, which progressed to marked generalized abdominal pain one day after admission.

On the second day of admission, abdominopelvic computed tomography (APCT) revealed ascites throughout the abdomen and destructive lymphadenopathy in the femoral and inguinal areas (Fig. 1). The patient was referred to Chungnum National University Sejong Hospital, where laboratory test results revealed no remarkable abnormalities (Table 1). VVse (Entelon, Hanlim Pharm) 300 mg/day (150 mg tablet twice daily) was administered to the patient on the 2nd day following the snakebite. Her symptoms

significantly improved on the 4th day, the 2nd day after VVse administration. On the 5th day after the snakebite, the 3rd day after VVse administration, ascites was no longer observed on abdominal ultrasound, and the swelling in the left leg improved, reaching only to the ankle. On the 7th day after the snakebite, the left leg swelling completely resolved, and APCT revealed no definite ascites in the abdomen (Fig. 1). Furthermore, laboratory test results revealed no remarkable changes (Table 1). On the 8th day of the snakebite, the patient was discharged from the hospital. VVse was administered for an additional 6 days after discharge. No specific findings were observed at the outpatient clinic 3 weeks after the snakebite.

The second case was a 69-year-old woman with no past medi-



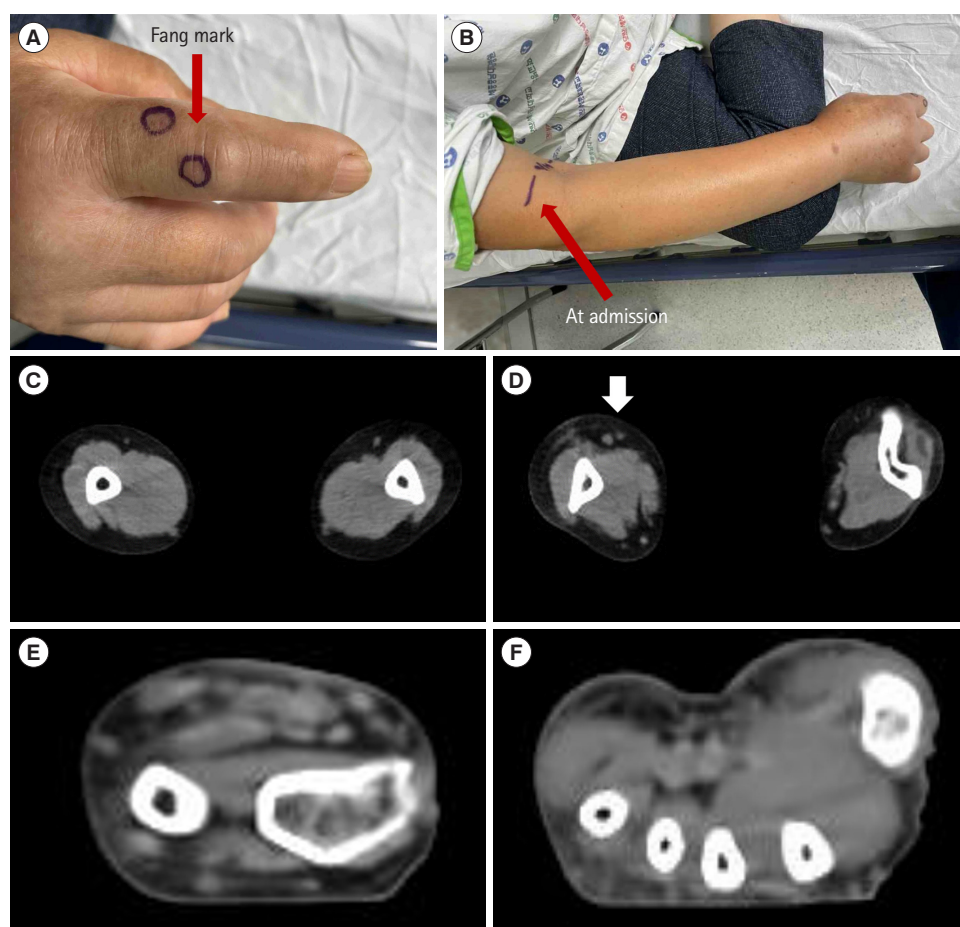
**Fig. 1.** Case 1. (A, B) Progression of left leg swelling after admission to the local hospital (red arrows). (A) At admission 10 minutes after the snakebite. At 75 minutes after the snakebite, the swelling progressed to the knee. (B) At 90 minutes after the snakebite, the swelling progressed to the proximal femur. (C–E) Abdominopelvic computed tomography was performed on the 2nd day after the snakebite. (C) Markedly progressed retroperitoneal fluid was identified (white arrow). (D) Ascites were observed in the pelvic cavity (white arrow). (E) Lymphadenopathy was identified in the left proximal femoral area (white arrow). Abdominopelvic computed tomography was performed on the 7th day after the snakebite and showed (F) markedly improved retroperitoneal fluid volume, (G) markedly improved ascites in the pelvic cavity, and (H) persistent lymphadenopathy at the proximal femoral area (white arrow).

**Table 1.** Laboratory findings of cases 1 and 2

Case	WBC (/μL)	Hemoglobin (g/dL)	CRP (mg/dL)	CPK (U/L)	PT (INR)	aPTT (sec)
Case 1						
Day 1	7,810	12.8	2.0	143	1.23	28.6
Day 2	4,040	10.2	1.0	110	1.07	31.7
Day 3	4,400	11.3	0.5	53	1.16	35.5
Day 5	4,600	12.6	0.3	46	1.03	33.1
Case 2						
Day 1	13,630	12.7	0.6	643	1.06	26.0
Day 2	14,500	11.4	1.3	1,500	1.06	24.9
Day 3	9,490	11.7	1.4	5,546	1.05	22.4
Day 5	6,200	12.7	0.2	1,922	1.01	29.4

WBC, white blood cell count; CRP, C-reactive protein; CPK, creatine phosphokinase; PT, prothrombin time; INR, international normalized ratio; aPTT, activated partial thromboplastin time.

cal history admitted for a snakebite on her right second finger. She arrived at the emergency department of our hospital 45 minutes following the snakebite, with severe local pain and swelling that progressed to the distal humerus of the right arm. Making a fist was challenging due to the swelling (Fig. 2). The local effect score was 13 (pain, 4; swelling, 3; ecchymosis, 2; time, 4). The patient also complained of visual disturbances with diplopia and dizziness. However, there was no history of bleeding from the gums, epistaxis, hemoptysis, hematemesis, melena, vaginal bleeding, or loss of consciousness. Laboratory test results revealed no remarkable abnormalities (Table 1). A skin allergy test for antivenom administration was positive, and the patient was deemed unsuitable for antivenom administration. Therefore, pyridostigmine (Mestinon, Korean Drug) 180 mg/day (60 mg tablet three times daily) and Wse (Entelon) 300 mg/day (150 mg tablet twice



**Fig. 2.** Case 2. (A, B) The fang marks and swelling progression of the right arm after admission. (A) Fang marks were identified on the right pointer finger (red arrow). (B) The patient arrived at the emergency department of our hospital 45 minutes after the snakebite. At admission, the swelling had progressed to the distal humerus (red arrow). (C–F) Arm computed tomography was performed to evaluate the degree of lymphadenopathy on the 5th day after the snakebite. (C) Lymphadenopathy was not observed in the middle region of the left humerus compared with the contralateral side. (D) Lymphadenopathy and a small amount of fluid were observed in the left distal humerus compared with the contralateral side (white arrow). (E) Individual muscles of a muscle group were swollen, and multiple lymphadenopathies were observed in the distal forearm. (F) Soft tissue swelling was observed in the right hand.

daily) were administered to relieve the neurological symptoms and improve arm swelling, respectively [7,8]. The symptoms significantly improved on the third day following the snakebite. On the 5th day, the right arm swelling recovered to near normal, and the laboratory test results revealed no unusual findings (Table 1). The patient was discharged on the 5th day and continued VVse for an additional 6 days, for a total of 11 days. No specific findings were observed at the outpatient clinic 3 weeks following the snakebite.

The primary complaints of patients with snake bites are local symptoms of pain, swelling, and necrosis in the bite area. Generally, antivenoms do not provide sufficient protection against venom-induced local tissue damage [1–6,9–11].

Snake venom delivery typically occurs subcutaneously or can be intramuscular, releasing toxins into the interstitial space [3–6]. Snake venom toxins interact with hyaluronic acid in the extracellular matrix, facilitating interstitial spread before entry into the vessels. This causes local damage to the vascular endothelium, resulting in local hemorrhage and edema and altered absorption characteristics of the damaged vessels. Viperid snake venoms are a rich source of metalloproteases. One of the most serious effects induced by metalloproteases is local hemorrhage including myonecrosis, blistering, coagulopathy, platelet effects, and proinflammatory activity.

From the interstitium, toxins diffuse through the extracellular matrix until they reach a vessel with a permeable endothelium, where they can be absorbed [3–6,12,13]. The permeability of the blood vascular endothelium decreases as toxin molecular size increases. Large molecules are absorbed primarily through the lymphatics, producing a fundamentally different toxicokinetic profile from that of smaller toxins, which can achieve direct access to the blood capillaries [13]. Viperid snake venoms are rich in large molecule toxins and possess a pharmacokinetic profile characterized by a rapid initial absorption phase followed by a complex and slow absorption process from the site of venom injection [3–6,12,13].

Viper bites produce more intense local reactions compared to other snakebites [1,2,6,10]. Swelling may become apparent within 15 minutes of the bite and becomes massive within 2 to 3 days, persisting for up to 3 weeks [12]. The swelling spreads rapidly from the site of the bite and may involve the entire limb and adjacent trunk owing to the action of hyaluronic acid and metalloproteases [11]. Regional lymphadenopathy may also develop as a result of the large molecule toxins and can hinder absorption of the retained fluid [10–13]. If the envenomed tissue is contained in a tight fascial compartment, such as the pulp space of the digits or anterior tibial compartment, ischemia will develop [10–13].

In case 1, the patient's leg swelling worsened rapidly, and ascites

and lymphadenopathy were confirmed on APCT. However, antivenom alone did not improve these local symptoms. A treatment modality that could effectively control the local effects and ascites is warranted for use in such cases. In case 2, the patient exhibited an allergy to antivenom and presented with neurologic symptoms. Antivenom administration was contraindicated, and systemic symptoms, such as coagulopathy, were expected. Although the neurologic symptoms improved with pyridostigmine, control of the arm swelling was challenging. Similar to the first case, this shows the need for a treatment modality that can safely and effectively control toxic local effects.

In these cases, after a snakebite, one patient exhibited improvement within 7 days, and the other improved within 5 days. In previous studies in Korea and Japan, only the length of stay due to local swelling was investigated [14,15]. Since these patients were discharged from the hospital before complete symptom resolution, the exact period of improvement was unknown [14,15]. However, the length of stay was more than 2 weeks when the local effect score was 13 or higher and even longer when antivenom was not administered [14,15].

In studies on the effects of VVse on snake venom, *Vitis vinifera* extract has shown its ability to neutralize viper venom [3,5,6]. VVse effectively inhibited the caseinolytic, fibrinogenolytic, and hyaluronidase activities of the venom and efficiently neutralized its hemorrhage-inducing, edema-inducing, and myonecrotic properties. Moreover, the extract partially inhibited the procoagulant activity of the venom and inhibited degradation of the alpha and beta chains of human fibrinogen. Therefore, the extract possesses potent anti-snake venom properties, especially against the local effects of viper bites.

In conclusion, VVse may be able to treat the local toxic manifestations safely and effectively following a snakebite. Studies with larger sample sizes and studies determining the optimal initial dose of VVse for snake venom are warranted to further verify its efficacy.

## ETHICS STATEMENTS

This study was approved by the Institutional Review Board of Chungnam National University Sejong Hospital (No. CNUSH IRB 2021-07-008). The requirement for informed consent was waived due to the retrospective nature of the study.

## CONFLICT OF INTEREST

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

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# Eosinophilic granulomatosis with polyangiitis presenting as recurrent myocardial infarction

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Dear Editor,

We present a case of deep clinical and educational interest, underlying the importance of a multidisciplinary approach in the diagnostic approach to chest pain. A 36-year-old Indian male patient presented to the emergency department complaining about episodes of oppressive chest pain over the past week. Physical examination showed normal chest and cardiac auscultation. An electrocardiogram (ECG) showed sinus bradycardia with no repolarization abnormalities. Cardiac troponin was elevated (high-sensitive troponin I [hs-TnI], 171 ng/L). The patient was affected by asthma, treated with beclomethasone/formoterol 100/6 µg one inhalation twice daily. He also reported allergic rhinitis, a previous allergic reaction to ketoprofen (cutaneous rash) and Raynaud syndrome. The patient conditions rapidly deteriorated due to acute cardiogenic shock and ECG modification with anterolateral ST-segment elevation. An urgent invasive coronary angiogram (ICA) was performed, showing a complete thrombotic left main occlusion, which was treated with angioplasty and two drug-eluting stents (Fig. 1). Echocardiography showed severe left ventricular dysfunction. A mild dermatitis after salicylic acid administration resolved with intravenous hydrocortisone bolus (1 g). Over the next few days, the clinical condition rapidly improved with recovery of normal ventricular function. The thrombophilia screening was negative. He was discharged on dual antiplatelet therapy (aspirin 100 mg and prasugrel 10 mg daily), as well as atorvastatin 40 mg and bisoprolol 1.25 mg daily. Two weeks later he returned to the emergency department with recurrent jaw and chest pain, responsive to sublingual nitrates. Cardiac troponin were elevated (hs-TnI, 106 ng/L), with no clear ECG abnormalities. An ICA was performed, showing a good angiographic result of the recent angioplasty and no other coronary stenosis. During the hospital stay, the patient experienced several anginal episodes, responsive to nitrates. Serial ECGs during chest pain showed ischemic alterations in different leads, suggesting different coronary territory involvement, with troponin level fluctuations. During a longer angina episode, an ICA was repeated, and coronary vasospasm of the circumflex artery were detected, with complete resolution after intracoronary nitroglycerin (Fig. 2). A diagnosis of vasospastic angina was made, and nitroglycerin and calcium channel blockers were added. However, several vasospastic anginal episodes still occurred on a daily basis. Cetirizine was added to the therapy, suspecting coronary ischemia secondary to allergic reaction (Kounis syndrome), without any effect on symptoms. Further investigations were made: laboratory tests revealed eosinophilia (4,390 cells/µL), increased C reactive protein (9.4 mg/L) and positive antinuclear antibodies (1:320).

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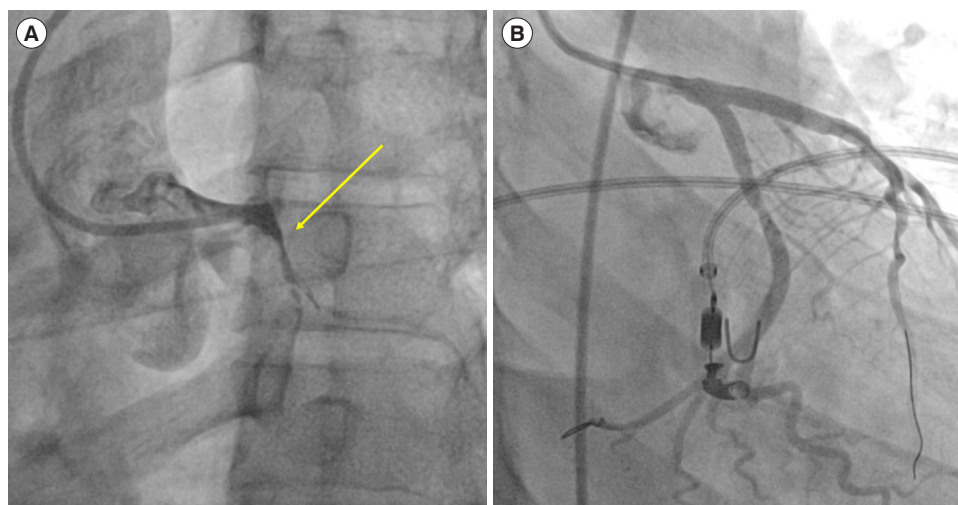
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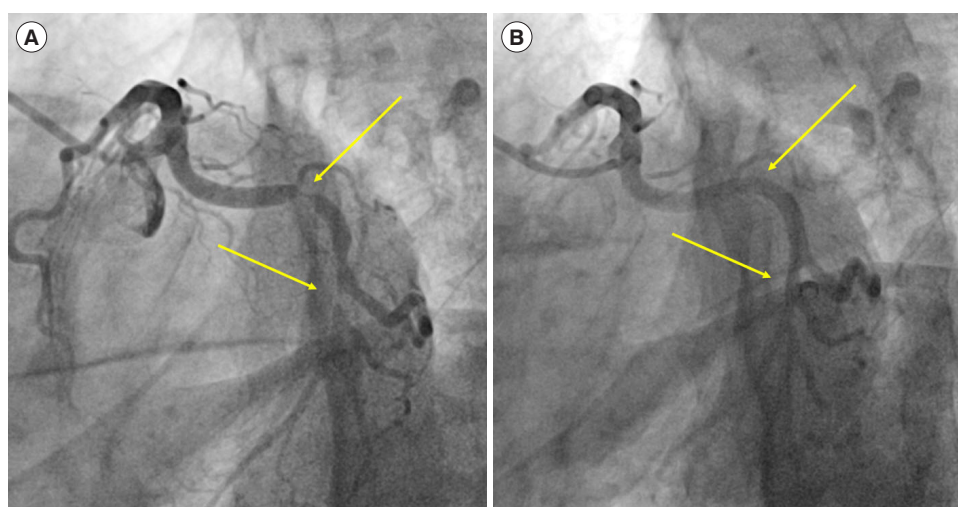
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**Fig. 1.** Coronary angiogram showing (A) left main occlusion (arrow) and (B) final result after angioplasty and implantation of two drug-eluting stents.



**Fig. 2.** Coronary angiogram showing (A) coronary vasospasm in the left circumflex artery (arrows) and (B) after intracoronary nitroglycerin infusion (arrows).

Other serological and immunological tests were negative, including proteinase 3 and myeloperoxidase antineutrophil cytoplasm antibodies (ANCA). An abdomen and chest computed tomography scan were performed and both were negative. Eosinophilia and a history of asthma led to suspected eosinophilic granulomatosis with polyangiitis (EGPA). The patient was treated with intravenous methylprednisolone 250 mg once daily for 3 days, followed by oral prednisone 1 mg/kg daily, with rapid and complete disappearance of the recurrent angina episodes. Intravenous cyclophosphamide was started, after sperm cryopreservation and continued for 6 months. A maintenance therapy with azathioprine was started.

The presented case demonstrates how coronary involvement in EGPA can mimic coronary artery disease. Only an accurate evalu-

ation of biomarkers and patient medical history correctly pointed the diagnosis towards an isolated coronary vasculitis causing myocardial infarction (MI) as an atypical manifestation of EGPA, prompting early immunosuppressive therapy pivotal for the patient survival. The patient did not fulfill the 1990 American College of Rheumatology (ACR) classification criteria for EGPA. Nevertheless, the presence of late-onset asthma and allergic rhinitis, eosinophilia greater than 10% on white cell differential count and the excellent clinical response after administration of high-dose corticosteroids confirmed the diagnosis of EGPA [1]. Asthma is the key clinical feature and is found in more than 90% of EGPA patients [2]. It usually presents about 8 to 10 years before the vasculitic phase [3]. Cardiac involvement is common and represents one of the most serious manifestations of EGPA. It accounts for

approximately one-half of deaths attributable to EGPA. Cardiac clinical manifestations include cardiomyopathy with signs of heart failure, pericarditis, cardiac rhythm abnormalities and—less frequently—coronary vasculitis [4]. Even if cardiac involvement in EGPA is well reported in the literature, isolated coronary vasculitis causing acute MI is a rare manifestation, especially at disease onset. Coronary vasculitis associated with EGPA may present with vasospasm, coronary thrombosis, and coronary ectasia [5]. To our knowledge, this is the first case reported in the literature where coronary vasculitis resulted in both thrombosis and vasospasm. At the time of first hospital admission, a left main complete thrombotic occlusion with associated vasospastic features was detected, and coronary vasospasm was also documented in the following admission. Interestingly, the patient did not experience recurrent angina during the first hospital stay. We believe this was due to the fact he received intravenous corticosteroids to treat a mild dermatitis after aspirin administration, temporarily improving coronary inflammation. Corticosteroids and immunosuppressive treatment are the mainstay of induction therapy in severe forms of EGPA and usually result in the recovery of impaired cardiac function. At 8-month follow-up, the patient was completely asymptomatic with normal biventricular function.

## ETHICS STATEMENTS

Written informed consents was obtained from the patient.

## CONFLICT OF INTEREST

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

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## AUTHOR CONTRIBUTIONS

Conceptualization: all authors; Data curation: GV, AF; Formal analysis: all authors; Investigation: all authors; Methodology: all au-

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# Optic nerve sheath diameter measurement by ultrasound after moderate traumatic brain injury

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Dear Editor,

We recently reviewed an article by Torabi et al. [1] in your journal concerning evaluation of optic nerve sheath diameter (ONSD) by ultrasound after moderate traumatic brain injury [1]. The article is noteworthy for its intriguing idea, but we would like to raise several concerns.

In the study, the authors utilized a 7.5 MHz linear probe to perform ONSD measurements in axial and coronal sections, most likely using the ultrasound B-scan technique. The B scan is very sensitive in detecting small optic nerve calcifications as in cases of optic nerve drusen, but it is not very reliable for measurements. [2–6].

We are aware that measurement of ONSD by ultrasound B scan has largely been conducted as a noninvasive method to detect increased intracranial pressure, but the presence of artefacts hinders these measurements [7–10]. Moreover, measuring the ONSD in the primary position is essential because altering the eye position can affect the quantity of cerebrospinal fluid surrounding the optic nerve, resulting in inaccurate ONSD measurements.

The study mentions that the authors performed the examination with closed eye lids, making it challenging to determine the gaze direction and potentially decreasing the image quality due to sound attenuation from the lids, creating less reliable results [11–13]. For this reason, it is advised to perform the examination with open eye lids and in the primary position after administering anesthetic eye drops, using methylcellulose as a coupling agent between the probe and the eye [14–17].

Therefore, in order to eliminate these anomalies and allow more accurate outcomes, it is recommended that standardized A scan techniques be utilized in future studies [18–20].

## ETHICS STATEMENTS

Not applicable.

## CONFLICT OF INTEREST

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

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