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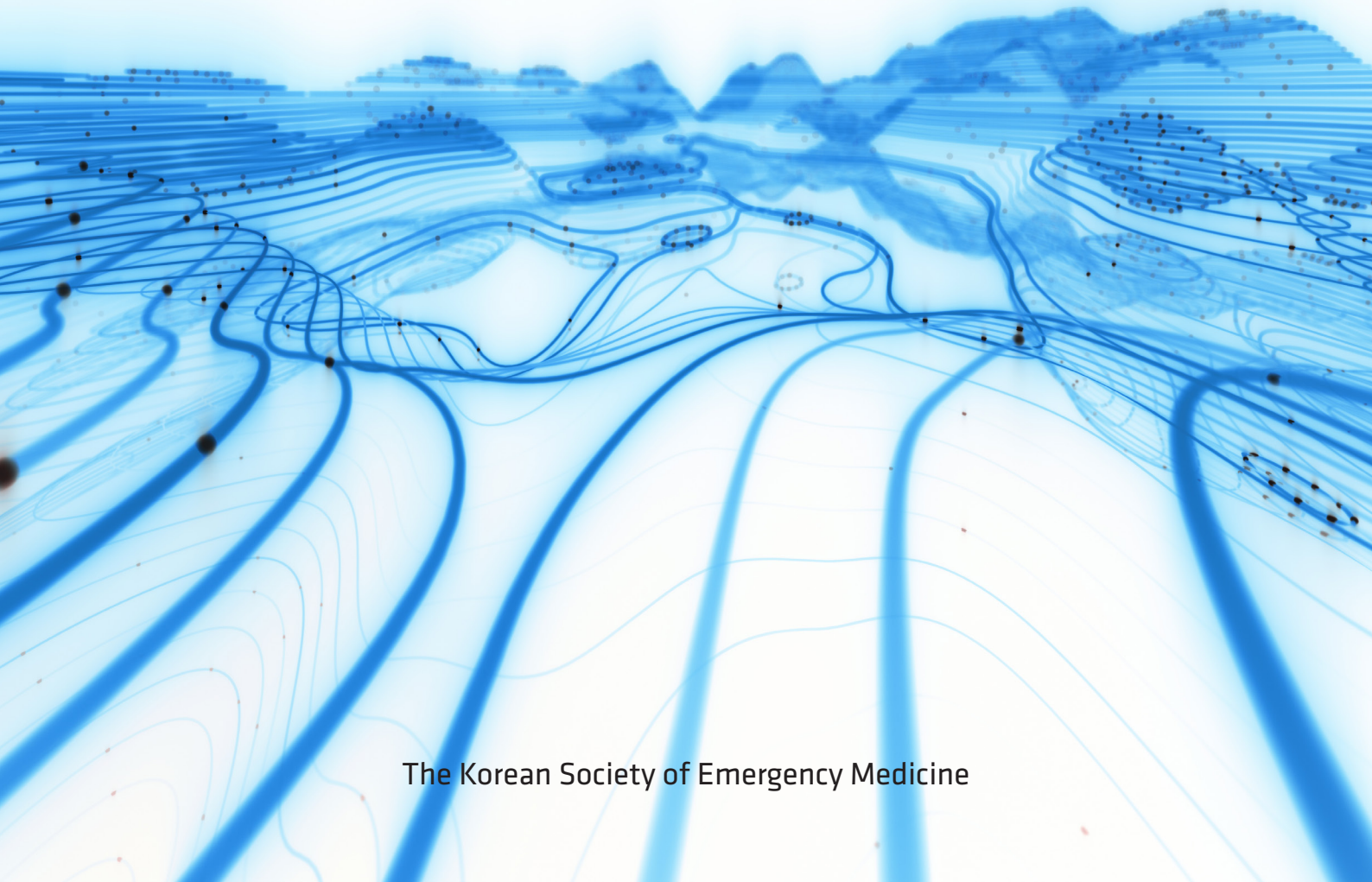

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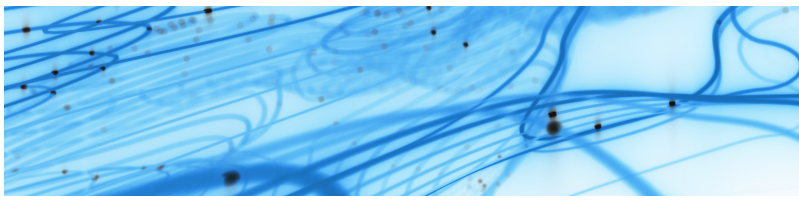

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Future of sepsis: perspective on diagnosis

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Editorial

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Sepsis is a global burden with no specific treatment.[1,2] Traditional treatment has focused on macrocirculation and hyperinflammation, but none has been successful.

Sepsis is not a single disease but can have many phenotypes.[3] Regarding oxygen supply and consumption, three systems are important: macrocirculation, microcirculation, and mitochondria.[4] Macrocirculation comprises cardiac function and arterial resistance (compliance). Fluid resuscitation and vasoactive treatment target cardiac output and blood pressure, which are components of the macrocirculation. Microcirculation is important since it is the last path for oxygen to reach the cell. Even though the optimal macrocirculation targets (blood pressure and cardiac output) can be achieved, the oxygen might not be able to be used by the cell due to microcirculatory and/or mitochondrial dysfunction. In this way, analysis is limited by lack of a widely and clinically used diagnostic tool to monitor microcirculation and mitochondrial function. At the investigational level, there are monitoring devices for those purposes.[5,6] Additional treatment options could be developed with advancement of real-time monitoring of these three components. As in Fig. 1, different combinations of sepsis are possible according to the three systems, and treatment could be more personalized rather than using the "one-size-fits-all" concept.

Another potential issue in sepsis is inflammation status. The traditional approach to reduce hyperinflammation (i.e., cytokine storm) is not optimal, and opposing treatments to enhance immune function are becoming more common.[7] For example, anti-programmed death-1 (anti-PD-1)/anti-programmed death ligand-1 (anti-PDL1), interferon gamma, and interleukin-7 are being investigated. However, the spectrum of immune status of patients is not categorical and can be rating scale and compartment specific. Therefore, additional diagnostic approaches are needed.

Medical treatment is dependent on the specific diagnosis, which requires knowledge of in-depth pathophysiology. To improve treatment of sepsis, its in-depth pathophysiology must be better understood for ideal diagnosis and personalized treatment.

CONFLICT OF INTEREST

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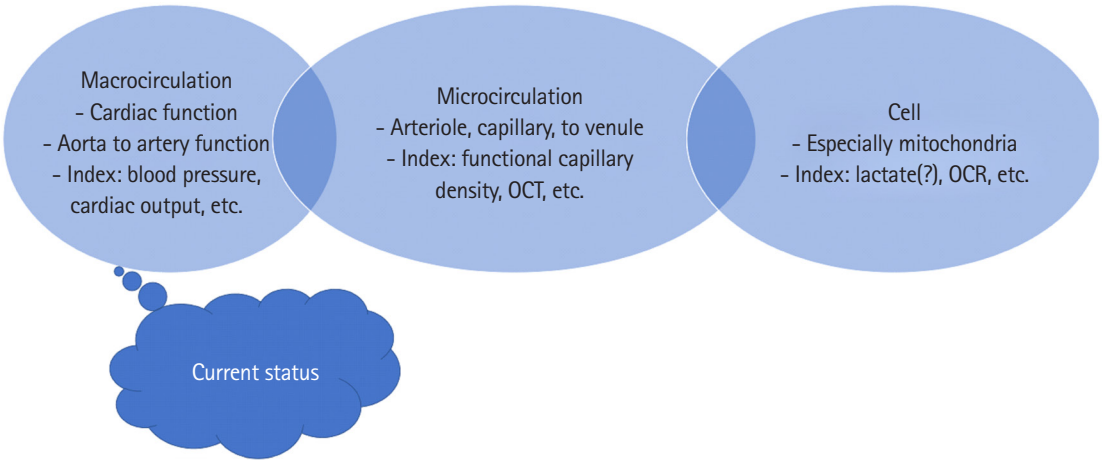
A



B

Phenotype	Macrocirculatory dysfunction	Microcirculatory dysfunction	Oxygen consumption dysfunction (mitochondrial dysfunction)	Current treatment
Type 1	O	O	O	Same, as usual
Type 2	O	O	X	Same, as usual
Type 3	O	X	X	Same, as usual
Type 4	O	X	O	Same, as usual
Type 5	X	O	O	Same, as usual
Type 6	X	O	X	Same, as usual
Type 7	X	X	X	Same, as usual
Type 8	X	X	O	Same, as usual

Only O or X?
How about Δ?
Actually, continuum!

Fig. 1. Conceptual model of types of sepsis. (A) Three systems of oxygen supply and consumption. (B) A variety of sepsis patients according to combinations of dysfunctions of the three systems. OCT, optical coherence tomography; OCR, oxygen consumption rate.

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Review Article

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Intra-arrest transesophageal echocardiography during cardiopulmonary resuscitation

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Determining the cause of cardiac arrest (CA) and the heart status during CA is crucial for its treatment. Transesophageal echocardiography (TEE) is an imaging method that facilitates close observation of the heart without interfering with cardiopulmonary resuscitation (CPR). Intra-arrest TEE is a point-of-care ultrasound technique that is used during CPR. Intra-arrest TEE is performed to diagnose the cause of CA, determine the presence of cardiac contraction, evaluate the quality of CPR, assist with catheter insertion, and explore the mechanism of blood flow during CPR. The common causes of CA diagnosed using intra-arrest TEE include cardiac tamponade, aortic dissection, pulmonary embolism, and intracardiac thrombus, which can be observed on a few simple image planes at the mid-esophageal and upper esophageal positions. To operate an intra-arrest TEE program, it is necessary to secure a physician who is capable of performing TEE, provide appropriate training, establish implementation protocols, and prepare a plan in collaboration with the CPR team.

Keywords Transesophageal echocardiography; Heart arrest; Cardiopulmonary resuscitation

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Capsule Summary

What is already known

The use of point-of-care ultrasound during cardiopulmonary resuscitation (CPR) has been suggested.

What is new in the current study

Intra-arrest transesophageal echocardiography can be used as a point-of-care ultrasound method to diagnose the cause of cardiac arrest, determine the presence of cardiac contractions, evaluate the quality of CPR, assist with catheter insertion, and explore the mechanism of blood flow during CPR.

How to cite this article:

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INTRODUCTION

Transesophageal echocardiography (TEE) is a diagnostic tool that can obtain images of the heart from its nearest location. It provides numerous types of echocardiographic information, including two-dimensional or three-dimensional images, M-mode, color flow imaging, Doppler studies, and related calculations, such as transthoracic echocardiography (TTE). Compared with TTE, TEE provides excellent echocardiographic windows to the heart regardless of the patient's body type. Despite its advantages, TEE has rarely been used in patients with cardiovascular emergencies in the emergency department (ED) when it was initially introduced into clinical practice. TEE in the ED has been used in urgent situations such as cardiac arrest (CA). Recent cardiopulmonary resuscitation (CPR) guidelines recommend or suggest the use of point-of-care ultrasound as a method to determine the reversible cause of CA during CPR, thus encouraging the use of echocardiography during the performance of advanced life support.[1,2]

TTE is an easy and simple method for point-of-care ultrasound during resuscitation. However, it is not suitable for close inspection of the heart while chest compressions are being performed. By employing TEE, rescuers can continuously observe the heart without interfering with CPR because the probe is located in the esophagus. Owing to the increasing use of TEE during resuscitation (intra-arrest TEE), the American College of Emergency Physicians and the American Society of Echocardiography have jointly published guidelines for point-of-care applications in CA resuscitation.[3] Since the publication of these guidelines, considerable experience has been accumulated with TEE during CPR. Korea, one of the first countries to use TEE in the ED, began employing TEE accordingly in 1992.[4] Recently, almost all EDs in Korea have been equipped with echocardiography machines; the remaining EDs are being prepared to support it. However, considering limitations in professional human resources and procedural time, it is unreasonable to conduct a comprehensive TEE study in the ED. By contrast, intra-arrest TEE as a point-of-care ultrasound is feasible in the ED and can be helpful in resuscitating patients who experienced CA. This review is intended to provide an overview of the practical use of intra-arrest TEE in emergency medicine.

INDICATIONS AND PREVIOUS EXPERIENCES

Intra-arrest TEE is performed to explore the mechanism of blood flow during CPR, diagnose the possible cause of CA, monitor the presence of cardiac contraction, assess the effectiveness of chest compression, guide catheter cannulation, and evaluate the complications of CPR. Table 1 summarizes the indications and objectives of intra-arrest TEE and the echocardiographic findings of intra-arrest TEE in the literature.[5-47]

PREPARATION FOR INTRA-ARREST TEE

Multiple factors should be considered when implementing intra-arrest TEE in the ED. These include the cost of the equipment; equipment maintenance, including probe disinfection; the input of additional personnel and technical training; evaluation of the operation quality; and collaboration with experts from other clinical fields, including cardiology.[48] For intra-arrest TEE, the TEE probe and related software must be purchased together with the echocardiography machine. The most appropriate area to place the echocardiography machine is a room in the resuscitation area. Drugs and devices for intensive monitoring and advanced life support, including airway support, defibrillation, and emergency medications, should be available at all times during TEE. According to Spaulding's classification for disinfection and sterilization of patient care items and equipment, the TEE probe is classified as a semi-critical instrument with an endoscope. Cleaning and disinfection after every use are required according to these guidelines.[49,50]

TEE should be performed by physicians who have (1) knowledge of cardiovascular anatomy and physiology, (2) knowledge of echocardiographic imaging, (3) proficiency and experience in performing TTE and TEE procedures, (4) knowledge required for interpretation of TEE results, and (5) knowledge of the management of TEE equipment and related instruments.[51] Considering these requirements, the guidelines recommend supervised performance and interpretation of at least 50 to 100 TEE procedures prior to the independent undertaking of TEE.[52-54] The American College of Emergency Physicians recommends a minimum of 10 proctored TEE examinations on live patients and simulation models with TEE-specific continuing medical education for the use of TEE in the ED for ultrasound-guided resuscitation during or after CA.[55] Therefore, emergency physicians performing TEE in the ED should have the qualifications for performing echocardiography, skills for TEE procedures, and competent TEE experience. Echocardiography is an operator-dependent procedure; therefore, the operator should conduct the procedure only after becoming certain that he or she can perform TEE on his or her own with consideration of the patient's safety. Lack of substantial training may result in misdiagnosis or misinterpretation of echocardiographic findings, possibly causing catastrophic outcomes.

INTRA-ARREST TEE PROCEDURE

A physician who is capable of performing TEE and is not part of

Table 1. Indications and findings of intra-arrest TEE in the literature

Study	Study type	No. of patients[a]	Indication/objective[b]	Main echocardiographic finding
Higano et al.[5] (1990)	Case report	2	Exploratory	Compression of RV and LV and closure of MV during compression
Kuhn et al.[6] (1991)	Case report	1	Exploratory	Opening of AV during thoracic compression with simultaneous closure of mitral and tricuspid valves
Porter et al.[7] (1992)	Prospective observational	17	Exploratory	Closure of MV during downstroke of chest compression and absence of correlation between MV flow and LV fractional shortening
Redberg et al.[8] (1993)	Prospective observational	20	Exploratory	MV opening during cardiac release, reduction of ventricular cavity size with compression, and atrioventricular regurgitation supporting the cardiac pump theory
Tucker et al.[9] (1993)	Prospective observational	5	Exploratory	Improved transmitral flow, end-decompression LV volume, and stroke volume with ACD CPR
Barton et al.[10] (1994)	Case report	1	Diagnostic	Massive pulmonary embolism as a cause of PEA
Ma et al.[11] (1994)	Case report	1	Complications	AV disruption complicating CPR
Pell et al.[12] (1994)	Prospective observational	18	Exploratory	Compression of all four cardiac chambers resulting in forward flow in pulmonary and systemic circulations, retrograde pulmonary vein flow, and incomplete MV closure
				Antegrade pulmonary vein flow and LV filling observed during relaxation phase
Pell et al.[13] (1994)	Prospective observational	7	Exploratory	Improved right heart compression, antegrade blood flow patterns, and LV filling during ACD CPR
Ma et al.[14] (1995)	Prospective observational	17	Exploratory	Presence of opened MV with forward mitral flow and backward pulmonary venous flow during chest compression, suggesting "LA pump"
Gilon et al.[15] (1996)	Case report	1	Exploratory	RV compression and tricuspid valve closure
Huemer et al.[16] (1996)	Case report	1	Exploratory	Closure of MV, opening of AV, and reduction of LV cross-sectional area during downstroke of chest compression
Van der Wouw et al.[17] (1997)	Prospective observational	48	Diagnostic	Cardiac tamponade (n = 6), myocardial infarction (n = 21), pulmonary embolism (n = 6), ruptured aorta (n = 1), aortic dissection (n = 4), papillary muscle rupture (n = 1), other diagnosis (n = 2), and absence of structural cardiac abnormalities (n = 7)
Hwang et al.[18] (1998)	Prospective observational	52	Diagnostic	Pericardial effusion (n = 10), aortic dissection (n = 5), occlusion of the mitral orifice by thrombus (n = 2), main pulmonary artery thrombus (n = 2), thrombotic occlusion of the prosthetic valve (n = 1), hypertrophic cardiomyopathy (n = 1), and aortic stenosis (n = 1)
Tsai et al.[19] (1999)	Case report	1	Diagnostic	Total tricuspid valve obstruction and massive pulmonary embolism
Comess et al.[20] (2000)	Prospective observational	36	Diagnostic	Pulmonary emboli in 9 of 25 patients (36%) with pulseless electrical activity as initial event
Hwang et al.[21] (2001)	Prospective observational	14	Exploratory	Deformation of the aorta at maximal compression site and increase in cross-sectional area of proximal aorta
Liu et al.[22] (2002)	Prospective observational	6	Exploratory	Closure of mitral and tricuspid valves with simultaneous opening of AV during chest compression
Memtsoudis et al.[23] (2006)	Retrospective observational	22	Exploratory	Thromboembolic events (n = 9), acute myocardial ischemia (n = 6), hypovolemia (n = 2), and pericardial tamponade (n = 2)
Lin et al.[24] (2006)	Prospective observational	10	Diagnostic	Myocardial infarction (n = 5), pulmonary embolism (n = 2), and severe hypovolemia and ventricular arrhythmia without specific pathology (n = 2)
Blaivas[25] (2008)	Case report	6	Diagnostic/monitoring	Identification of VF in patients with asystole on ECG
Kim et al.[26] (2008)	Prospective observational	10	Exploratory	Retrograde flow to LA and forward blood flow to aorta on LV contrast echocardiography during compression phase
Hwang et al.[27] (2009)	Prospective observational	34	Exploratory	Significant narrowing of LV outflow tract or aorta during compression phase
Weidman et al.[28] (2014)	Case report	1	Exploratory	Formation of multiple thrombi in heart and descending thoracic aorta during CA
Fair et al.[29] (2016)	Prospective observational	10	Guiding catheter cannulation	ECMO guidewire placement and cannula positioning
Liu et al.[30] (2016)	Prospective observational	20	Exploratory	Cardiac effect at beginning of CA, faded with time, making the thoracic pump dominant mechanism during prolonged CPR
Arntfield et al.[31] (2016)	Retrospective observational	23	Diagnostic/feasibility of TEE by emergency physicians	High degree of feasibility and clinical utility of ED-based TEE

(*Continued on the next page*)

Table 1. (Continued)

Study	Study type	No. of patients[a]	Indication/objective[b]	Main echocardiographic finding
Catena et al.[32] (2019)	Retrospective observational	19	Outcome prediction	LV outflow tract opening associated with successful CPR
Fair et al.[33] (2019)	Prospective interventional	25	Efficacy of TEE on pulse check time	Shorter pulse check times with TEE compared with TTE
Kim et al.[34] (2019)	Retrospective observational	20	Exploratory	Measurement of compression depth at RV free wall and calculation of compression velocity
Lee et al.[35] (2019)	Case report	1	Complications	Acute aortic dissection complicating CPR
Teran et al.[36] (2019)	Prospective observational	21	Diagnostic/CPR quality	Identification of pseudo-PEA and fine VF, determination of reversible pathology, and optimization of CPR quality
Giorgetti et al.[37] (2019)	Case report	1	Guiding catheterization	Monitoring of mechanical chest compression performance and guiding cannulation for ECPR
Long et al.[38] (2020)	Case report	1	Monitoring cardiac status	Monitoring of CA due to anaphylaxis
Merlin et al.[39] (2020)	Case report	1	Trial of out-of-hospital TEE	Report of initial case of out-of-hospital TEE
Jung et al.[40] (2020)	Retrospective observational	158	Diagnostic/prediction of outcome	Total of 40 patients (25.3%, TEE positive group) with specific TEE findings, including possible causes of CA (n = 31, 19.6%) and sequelae of CA (n = 9, 5.7%)
				Positive TEE findings were associated with poor resuscitation outcomes
Kim et al.[41] (2020)	Case report	1	Diagnostic	Paradoxical embolism of right heart thrombi visualized on TEE during CPR
Orihashi[42] (2020)	Case report	4	Guiding catheterization	Monitoring chest compressions, guiding catheter insertion, and assisting pericardiocentesis
Rublee et al.[43] (2020)	Case report	1	Diagnostic	Cardiac tamponade and type A aortic dissection
Kim et al.[44] (2021)	Retrospective observational	45	Diagnostic	Diagnosing aortic dissection as cause of CA
Poppe et al.[45] (2021)	Case report	1	Diagnostic	Massive intracardiac thrombus and subsequent thrombolysis
Horowitz et al.[46] (2021)	Case report	1	Diagnostic	Clot in transit in RA and thrombolysis
Jung et al.[47] (2022)	Retrospective observational	97	Evaluation of intracardiac shunt	Assessment for presence of right-to-left shunt during CPR

TEE, transesophageal echocardiography; RV, right ventricle; LV, left ventricle; MV, mitral valve; AV, aortic valve; ACD, active compression decompression; CPR, cardiopulmonary resuscitation; PEA, pulseless electrical activities; LA, left atrium; VF, ventricular fibrillation; ECG, electrocardiogram; CA, cardiac arrest; ECMO, extracorporeal membrane oxygenation; ED, emergency department; TTE, transthoracic echocardiography; ECPR, extracorporeal cardiopulmonary resuscitation; RA, right atrium.
[a]Number of patients only includes those who underwent TEE during CA. [b]Exploratory, determination of mechanism of blood flow during cardiopulmonary resuscitation; Diagnostic, diagnosis of cause of CA.

the CPR team is required for the intra-arrest TEE procedure. Intra-arrest TEE is usually initiated after endotracheal intubation is complete. The patient in CA is not able to swallow the TEE probe; therefore, the operator must push the TEE probe into the esophagus. Before insertion of the TEE probe into the esophagus, the operator initially checks whether the probe is located behind the endotracheal tube and then bends the probe tip (anteflexion position) and pushes it into the back of the pharynx. When the TEE probe reaches the pharynx, it is inserted into the esophagus by straightening (unlocked position) and pushing the tip of the probe. If resistance is sensed while inserting the probe, the probe tip is not inserted into the esophagus. Insertion with excessive force may cause damage to the hypopharynx or upper esophagus.[56,57] Care should be taken not to dislodge the endotracheal tube during TEE.

IMAGING PROTOCOL AND VIEWS FOR INTRA-ARREST TEE

The protocol for intra-arrest TEE includes a quick scan to assess the possible cause of CA and the presence of cardiac contraction, assessment of CPR quality, monitoring of resuscitation measures, and guidance of catheter cannulation. To perform an initial scan immediately after probe insertion, the mid-esophageal (ME) four-chamber view, ME long-axis (ME LAX) view, ME ascending aorta short-axis (SAX) view, ME ascending aorta LAX view, descending aorta SAX view, and upper esophageal aortic arch LAX view are obtained in order (Fig. 1).[40] Transgastric views during chest compressions are not recommend because the forceful anterograde or retrograde flexion position for the transgastric views may cause injury to the esophagus or stomach.[58,59] After quick observation of the heart and great vessels, a TEE probe with a four-chamber view is placed at the ME level to monitor for cardiac movement

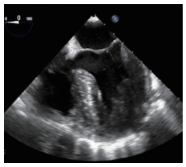
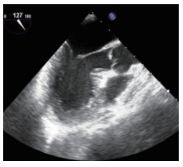
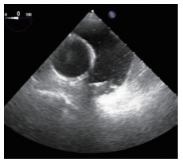
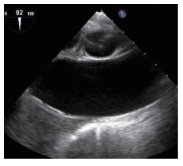
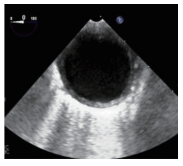
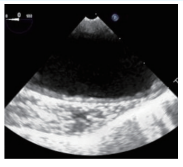
Two-dimensional imaging plane	Acquisition position (transducer angle)	Structures imaged	Cause of cardiac arrest to be observed
 ME four-chamber view	30–35 cm from incisor (approximately 0°–10°)	RA, RV, LA, LV, MV, AV, TV	Cardiac tamponade, clots in transit, thrombi in LA or LV, papillary muscle rupture, and septal rupture Presence of cardiac contraction
 ME long-axis view	30–35 cm from incisor (approximately 120°–140°)	LA, LV, LVOT, MV, AV, aortic root, and RVOT	Cardiac tamponade, aortic dissection, thrombi in LA or LV, papillary muscle rupture, and septal rupture Presence of cardiac contraction
 ME ascending aorta short-axis view	30–35 cm from incisor (approximately 0°–30°)	Ascending aorta, main and bifurcation of pulmonary artery, and SVC	Aortic dissection and pulmonary embolism
 ME ascending aorta long-axis view	30–35 cm from incisor (approximately 90°–110°)	Ascending aorta and right pulmonary artery	Aortic dissection and pulmonary embolism
 Descending aorta short-axis view	25 cm or deeper from incisor (approximately 0°–10°)	Descending aorta, left thorax	Aortic dissection Left pleural effusion
 Upper esophageal aortic arch long-axis view	25–30 cm from incisor (approximately 0°–10°)	Aortic arch Innominate vein	Aortic dissection, aneurysm, and atheromatous ulcer

Fig. 1. Suggested intra-arrest transesophageal echocardiography imaging planes and the corresponding structures or pathologies imaged. ME, mid-esophageal; RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle; MV, mitral valve; AV, aortic valve; TV, tricuspid valve; LVOT, left ventricular outflow tract; RVOT, right ventricular outflow tract; SVC, superior vena cava.

and assist resuscitation measures. When catheterization is required for resuscitative measures, such as employing a central venous catheter, extracorporeal membrane oxygenation, or resuscitative endovascular balloon occlusion of the aorta (REBOA), ME bicaval view and the descending aorta SAX and LAX view are optimal for visualizing the vena cava or aorta. After the return of spontaneous circulation, a comprehensive examination of cardiac function, morphology, and regional-wall motion is needed.

FINDINGS OF INTRA-ARREST TEE

The diagnostic sensitivity, specificity, and positive predictive value of TEE for the cause of CA were reported to be 93%, 50%, and 87%, respectively.[17] One-fourth of the patients who underwent intra-arrest TEE showed specific evidence associated with CA. Such evidence is associated with poor resuscitation outcome.[40] The common causes of CA confirmed by TEE are cardiac tamponade, aortic dissection, pulmonary embolism, and intracardiac thrombi. Cardiac tamponade is easily diagnosed and appears as a

large amount of pericardial effusion with the collapse of the right ventricle (RV) in ME views (Fig. 2). A large pericardial effusion and/or left pleural effusion may be a sign of aortic rupture (Fig. 3). Aortic dissection can be diagnosed by the presence of an intimal flap in the ascending aorta, aortic arch, and descending aorta views (Fig. 4). High suspicion or diagnosis of pulmonary embolism is possible when thrombi are observed in the right atrium, RV, or pulmonary artery (Figs. 5, 6). Intracardiac or disseminated thrombi, observed as echogenic densities in the left-side cardiac chambers and/or the aorta without right heart thrombus, is a sequela of CA (Fig. 7). During a quick scan of the possible causes of CA, cardiac contraction and movement during chest compressions can be observed. Fibrillary or mechanical contractions of the ventricle can be observed during ventricular fibrillation or pulseless electrical activity (Supplemental Video 1). Catheterizations for in-

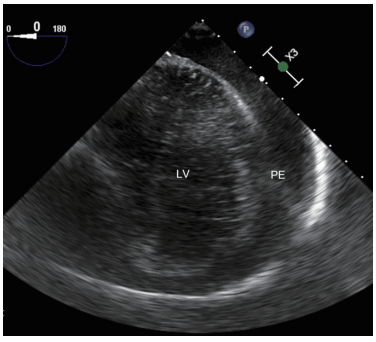


Fig. 2. Cardiac tamponade. The mid-esophageal view shows a large amount of pericardial effusion (PE) surrounding the left ventricle (LV).

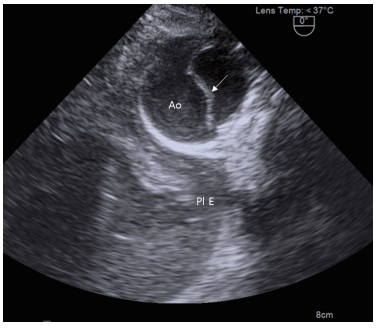


Fig. 3. Ruptured aortic dissection. A dissecting flap (arrow) and left pleural effusion (Pl E) are noted on the descending aorta (AO) short-axis view.

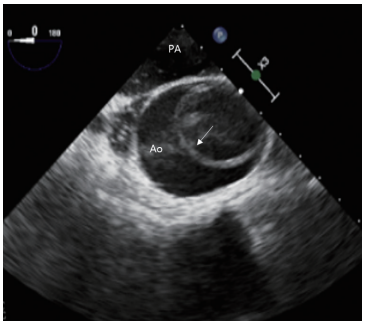


Fig. 4. Aortic dissection. The mid-esophageal ascending aorta short-axis view shows a dissecting flap (arrow) in the ascending aorta (Ao). PA, pulmonary artery.

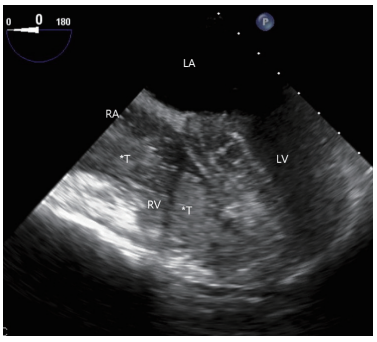


Fig. 5. Thrombi (T*) in the right-sided chambers. Echogenic densities occupying the right atrium (RA) and the right ventricle (RV) on the mid-esophageal four-chamber view suggest pulmonary embolism as a possible cause of cardiac arrest. LA, left atrium; LV, left ventricle.

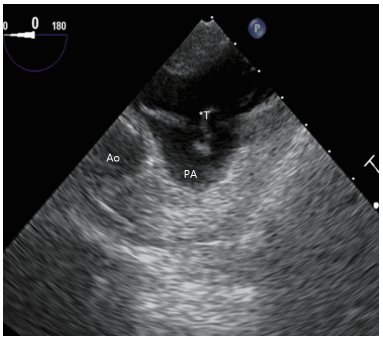


Fig. 6. Thrombi (T*) in the pulmonary artery (PA). The mid-esophageal view for the PA shows echogenic densities in the main and right PA. Ao, ascending aorta.

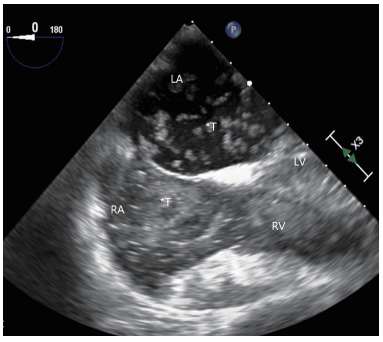


Fig. 7. Intracardiac thrombi (T*). Echogenic densities with variable sizes are noted in all cardiac chambers suggesting sequelae of prolonged cardiac arrest. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

terventional measures, such as REBOA or extracorporeal CPR, can be assisted by intra-arrest TEE.[29,60] Cardiac movement, including compression of the cardiac chambers and valvular motion, can be continuously monitored during TEE.[7,8,14,21] Kinetic analysis of chest compressions can be performed by measuring the excursions of the free wall of the RV.[34] An intracardiac shunt or paradoxical embolism can be detected during intra-arrest TEE.[41,47]

SAFETY OF INTRA-ARREST TEE

TEE is relatively safe. The overall complication rate of diagnostic and intraoperative TEE ranges from 0.18% to 2.8%, and the mortality rate is less than 0.01% to 0.02%.[61-63] However, no study has reported the safety of intra-arrest TEE. From our experience (unpublished data), intra-arrest TEE was successfully performed with no complications in 179 of 183 patients (97.8%) who experienced out-of-hospital CA. Failure of TEE probe insertion into the esophagus occurred in three patients (1.6%), while vallecular injury was confirmed in one patient (0.5%) after intra-arrest TEE. The electrical safety of using TEE during transthoracic defibrillation remains controversial.[64] Operator injury or equipment failure was not reported during transthoracic defibrillation. No study has reported the harmful effects of transthoracic defibrillation on operators or patients when a TEE probe is inserted. However, the effect of defibrillation on TEE machines has not yet been evaluated.

CONCLUSION

TEE is now widely practiced not only by cardiologists, but also by doctors who manage patients with cardiovascular disorders, including emergency physicians, intensivists, and anesthesiologists. Excellent imaging windows, easy accessibility, and high portability have enabled TEE to be a point-of-care imaging modality during CA in the ED. Intra-arrest TEE facilitates the diagnosis of the CA cause, enables the evaluation of cardiac contractions and CPR quality, and aids in catheter insertion for therapeutic procedures. Trained experts, protocols, coordination, and equipment maintenance are essential for the successful application of an intra-arrest TEE program in the ED. Future research should evaluate the effect of intra-arrest TEE on resuscitation outcomes in patients with CA.

SUPPLEMENTARY MATERIAL

Supplementary Video 1. Illustrative case of ventricular fibrillation observed on intra-arrest transesophageal echocardiography. The mid-esophageal four-chamber view shows fine fibrillary contraction of the left ventricle and mitral valve movement.
Supplementary material is available at https://doi.org/10.15441/ceem.22.399.

CONFLICT OF INTEREST

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

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AUTHOR CONTRIBUTIONS

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Review Article

The 2022 monkeypox outbreak in nonendemic countries: a review for the emergency department clinician

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Since May 2022, monkeypox (MPX) cases have been reported from several European countries, and this outbreak rapidly spread globally. Although MPX is not a new disease, most clinicians in nonendemic countries are unfamiliar with it. In addition, this current outbreak, unlike previous outbreaks in Africa, shows unique features in terms of epidemiology, transmission routes, and clinical manifestation. Most cases were men who have sex with men, had no travel history to an MPX endemic area, and presented with anogenital lesions, suggesting human-to-human transmission via close contact during sexual activity. In the emergency department setting, rapid identification of suspected cases and implementation of effective infection control and preventive measures are critical for preventing further transmission to healthcare workers and other patients. Emergency department clinicians should be aware of the clinical presentations of MPX and be alert to patients presenting with fever and vesicular rash or sexually transmitted disease-associated rash, especially among those with travel history to countries reporting an MPX outbreak. This brief review provides current information of MPX to help emergency department clinicians understand the epidemiology, transmission, clinical manifestation, diagnosis, treatment, and infection prevention and control of MPX.

Keywords Monkeypox; Disease outbreaks; Infection control

Capsule Summary

What is already known

Since the first human case of monkeypox (MPX) in 1970 in the Democratic Republic of Congo, sporadic outbreaks mainly in African regions and occasional cases and limited outbreaks linked to travel or importation of African animals have been reported. Since May 2022, numerous cases of MPX were reported from several nonendemic countries and this outbreak rapidly spread.

What is new in the current study

This brief review provides the current information of MPX to help emergency department clinicians understand the epidemiology, transmission, clinical manifestation, diagnosis, treatment, and infection prevention and control of MPX.

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INTRODUCTION

Monkeypox (MPX) is a zoonotic viral disease caused by the *Monkeypox virus* (MPXV). Since the first human case of MPX from the Democratic Republic of Congo in 1970, most human cases have been reported in West and Central Africa.[1] Outside of Africa, MPX caused an outbreak in 2003 in the United States, linked to importation of infected rodents from Ghana, and a few sporadic travel-related cases in the United States, United Kingdom, Israel, and Singapore.[2] In May 2022, several European countries and the United States reported atypical cases of MPX, which rapidly spread globally. Most cases were men who have sex with men without any documented history of travel to an MPX endemic area. Between January 1 and August 22, 2022, there were 41,664 confirmed cases of MPX, and 12 deaths reported from 96 countries, with approximately 99% of cases reported outside of Africa.[3] This unprecedented outbreak shows different features in terms of epidemiology and clinical manifestations compared to previous reported MPX in endemic areas.[3-6]

Emergency department clinicians should be aware of the current epidemiology and clinical symptoms and signs of MPX for rapid identification of suspected cases. This brief review aims to provide current information on MPX to help emergency department clinicians understand the epidemiology, transmission, clinical manifestations, diagnosis, treatment, and infection prevention and control of MPX. An overview of MPX is presented in Table 1.

EPIDEMIOLOGY OF THE 2022 MPX OUTBREAK

A World Health Organization report published August 24, 2022 shows an overwhelming predominance of affected men (98.2%) with a median age of 36 years (interquartile range, 30–43 years). Among cases with known data on sexual orientation, 95.8% were identified as men who have sex with men. A sexual encounter was the most common type of transmission (82.1%), and the majority of cases (60.6%) were likely exposed in a party setting via sexual contact. Of those cases with known HIV status, 45% were HIV

Table 1. Overview of MPX for the emergency department clinician

Category	Description
Causative agent	*Monkeypox virus*, a double-stranded DNA virus, is a member of the *orthopoxvirus* genus within the Poxviridae family
Transmission	Animal-to-human transmission: direct or indirect contact with live or dead animals Human-to-human transmission: • Direct contact with infected lesions or body fluids, respiratory droplets during close and prolonged face-to-face contact, or contact with contaminated objects such as clothing or linens • Direct and prolonged skin-to-skin contact during sexual activity[a]
Clinical feature	Incubation period: 5–21 days (typically 6–13 days following exposure) Typical symptoms and signs observed in past outbreaks in the endemic regions: • Initial prodrome followed by appearance of characteristic skin lesions, typically showing a centrifugal distribution • Skin lesions were often synchronous in their development and in rash progression (macule → papule → vesicle → pustule → crust) Atypical presentations observed in the 2022 outbreak: • Relative mildness or absence of prodromal symptoms • Presence of only a few or even a single lesion that originates in the genital or perineal/perianal region • Rectal symptoms (rectal pain or rectal bleeding) have been frequently reported
Diagnosis	Laboratory confirmation: PCR analysis of specimens collected from infected lesions Recommended specimen type: skin lesion material, including swabs of lesion exudate, roofs from more than one lesion, or lesion crusts
Treatment	Currently there is no treatment approved specifically for MPX Primarily supportive care with pain control, hydration, and management of complications Two antivirals, tecovirimat and brincidofovir, approved in the United States for treatment of smallpox, have been demonstrated to be effective against MPX
Vaccination	JYNNEOS vaccine, a third-generation vaccine FDA-approved for prevention of MPX infection PPV: individuals and healthcare workers at high risk of exposure, clinical laboratory personnel performing diagnostic testing for MPX, and outbreak response team members PEPV: close contacts of cases, ideally within 4 days of first exposure (and up to 14 days in the absence of symptoms)
Infection control of MPX in healthcare settings	Standard, contact, and droplet precautions should be applied when caring for suspected or confirmed cases of MPX Isolation of suspected or confirmed cases of MPX: a separate room with a dedicated toilet Personal protective equipment of healthcare workers: gloves, gown, eye protection, and respirator

MPX, monkeypox; PCR, polymerase chain reaction; FDA, US Food and Drug Administration; PPV, Primary preventive (preexposure) vaccination; PEPV, Postexposure vaccination.

[a]Primary mode of transmission observed in the 2022 outbreak.

positive. Although a small proportion of cases has been reported among health workers (n = 256), most were infected in the community.[3] To date, all cases identified in nonendemic countries whose samples were confirmed by polymerase chain reaction have been identified as being infected with the West African clade,[3] which is often associated with milder disease than the Congo basin clade.[7] Some outbreak clade mutations have been identified in proteins involved in virus transmission and virulence.[8]

TRANSMISSION AND VIRAL SHEDDING

Before the current outbreak, virus transmission through direct or indirect contact with live or dead animals was assumed to be the main factor for human MPX infections. Human-to-human transmission occurs primarily through direct contact with infected lesions or body fluids, respiratory droplets during close and prolonged face-to-face contact, or contact with contaminated objects such as clothing or linens.[7] However, in the 2017–2018 MPX outbreak in Nigeria, several unique findings were identified compared to previous MPX outbreaks in the African region.[9,10] Most of the infected cases were young men without exposure to infected animals and presented with genital ulcers, similar to cases in the current outbreak in nonendemic countries. In a study published in 2019, Nigerian researchers suggested the possibility of sexual transmission, but this hypothesis has not received considerable attention.[10] In the 2022 outbreaks, human-to-human transmission is occurring at an unprecedented and large scale, and the primary mode of transmission is direct and prolonged skin-to-skin contact during sexual activity.[3,4] In a large case study series, MPXV DNA was found in the semen of 29 of 32 people.[4] Another study reported frequent MPXV DNA in clinical samples including saliva, semen, rectal swab, urine, and feces from infected patients.[11] However, the infectious potential of these bodily fluids and their potential role in disease transmission are uncertain. In the pandemic of COVID-19, there are growing concerns about MPX potentially being transmitted through aerosols. A previous study of an MPX case in the UK healthcare workers (HCWs) in 2018 suggested that MPX can become aerosolized, particularly during certain activities like changing contaminated bedding.[12] However, in existing epidemiological investigations, no cases of long-range airborne transmission have been reported. A person is considered infectious from symptom onset until all skin lesions have crusted, those crusts have separated, and a fresh layer of healthy skin has formed underneath.[7] Although a recent study in France has suggested that asymptomatic MPX spread is contributing to the global outbreak, the infectiousness of asymptomatic individuals is uncertain.[13]

CLINICAL PRESENTATION OF MPX IN THE CURRENT OUTBREAK

The incubation period ranges from 5 to 21 days but is typically 6 to 13 days following exposure.[1,7] Historically, patients with MPX have typically presented with prodromal symptoms, including fever, headaches, chills, malaise, and lymphadenopathy, followed by development of a macular rash starting from the face and spreading across the entire body.[1,7] Involvement of the genital area was reported in an old study in less than 30% of affected patients.[14] The skin lesion of MPX usually progresses through macules, papules, vesicles, pustules, and scabs. Unlike chickenpox, the lesions typically present at the same stage. The number of skin lesions exceeds 100 in 49% to 66% of patients, with more than 1,000 lesions in 17.5% of cases.[14,15] Complications in endemic countries include encephalitis, secondary skin bacterial infections, dehydration, conjunctivitis, keratitis, and pneumonia.[1,7]

In the current 2022 outbreak, the majority of cases show atypical presentations, with rash in fewer regions of the body, in particular the genital and perianal areas, without spread to other body regions and with a relative mildness or absence of prodromal symptoms.[3-6] In the observational study of 528 MPX cases from 16 countries, 95% presented with a rash and 73% had anogenital lesions.[4] Most of the patients (64%) had 10 or fewer lesions, with 10% having a single genital lesion. Although there were no fatalities within the cohort, 13% were hospitalized for management of anorectal pain or bacterial superinfection. Additionally, two types of serious complications including epiglottitis and myocarditis were reported. The case fatality ratio of monkeypox has historically ranged from 1% to 11% in the general population and has been higher among young children.[1,7] In this outbreak, as of August 10, 2022, four deaths related to MPX have been reported outside the African region (two in Spain, one in Brazil, and one in India). In two cases, deaths have been linked to viral encephalitis, and some patients had underlying immune compromising conditions.[16] Table 2 summarizes data on the demographic and clinical characteristics of patients with MPX infection in the 2022 outbreak.[4-6]

DIAGNOSIS AND TREATMENT OF MPX

It is important to be aware of the clinical presentations of MPX that have been described in the ongoing 2022 outbreak. When there is clinical suspicion for MPX, clinicians should ask about travel history and close contact with people with a similar rash or suspected or confirmed MPX infection. Particularly, clinicians should consider MPXV in differential diagnoses of sexually transmitted diseases presenting with genital lesions. Swabbing of a lesion exu-

Table 2. Demographic and clinical characteristics of patients with monkeypox infection in the 2022 outbreak

Variable	International case series	Spain	London
Study	Thornhill et al.[4]	Tarin-Vicente et al.[5]	Patel et al.[6]
No. of cases	528	181	197
Age (yr), median (range)	38 (18–68)	37 (19–58)	38 (21–67)
Male sex (%)	> 99	97	100
Sex orientation (%)	Homosexual (96)	Homosexual or bisexual (92)	Homosexual or bisexual (99.5)
HIV positive (%)	41	40	35.5
Incubation period (day), median (range)	7 (3–20)	7 (1–19)	Not reported
Common symptom (%)	Rash or skin lesion (5), fever (62), lymphadenopathy (56), lethargy (41), myalgia (31), headache (27), pharyngitis (21), proctitis or anorectal pain (14)	Rash or skin lesion (100), lymphadenopathy (85), fever (72), headache (53), sore throat (36), proctitis (25)	Rash or skin lesion (100), fever (61.9), lymphadenopathy (57.9), rectal pain (36.0), myalgia (31.5), sore throat (16.8)
No. of skin lesions (%)	< 5 (39) 5–20 (46)	< 3 (12) 3–20 (80)	2–10 (51.8) 11–50 (18.3)
Site of skin lesion (%)	Anogenital area (73), trunk and extremities (55), face (25), palms or soles (10)	Hands and feet (60), trunk and extremities (57), genital (55), perianal (36), perioral (28), oral ulcer (25)	Genital (56.4), anus, or perianal area (41.6), face (36.0), trunk (35.5), extremities (37.6), hand and feet (28.4), oropharyngeal (13.7)
Outcome	No death	No death	No death

date or crust specimen is considered the best sampling method to obtain a rapid and definite diagnosis of MPX. The nucleic acid of the virus could be also retrieved in blood, urine, upper respiratory tract excretions, and seminal fluid.[17] The treatment of MPX is primarily supportive with pain control, hydration, and management of complications. Antibiotics may be necessary in patients with a secondary bacterial skin infection, pneumonia, or conjunctivitis. There are no treatments specifically for MPXV infections. However, two antivirals, tecovirimat and brincidofovir, approved in the United States for treatment of smallpox, have been demonstrated to be effective against *orthopoxviruses* (including MPX) in animal models.[18] In Korea, tecovirimat is recommended for severe cases of MPX or immunocompromised persons. Additionally, cidofovir and vaccinia immune globulin may be considered for severe cases.[18]

INFECTION PREVENTION AND CONTROL OF MPX IN HEALTHCARE SETTINGS

A combination of standard, contact, and droplet precautions should be applied in healthcare settings when caring for suspected or confirmed cases of MPX. Additionally, because of the theoretical risk of airborne transmission of MPXV, airborne precautions should be applied based on risk assessment. The patient should be required to wear a medical mask and placed in an isolated room with a dedicated toilet. No special air handling is required, but any procedures likely to spread oral secretions should be performed in an airborne infection isolation room. Skin lesions of the patients should be covered to the extent possible to minimize contact risk with others. Isolation precautions should be continued until all lesions have resolved and a fresh layer of skin has formed.[19]

HCWs caring for confirmed or suspected MPX patients or handling specimens for diagnosis should use personal protective equipment, including gloves, gown, eye protection, and respirator. Dedicated footwear also can be used. For environmental infection control, standard cleaning and disinfection procedures are sufficient, but soiled laundry should be handled with gloves to avoid contact with lesion material and never be shaken or handled in a manner that may disperse infectious material.[19]

The probability of exposure to MPXV for HCWs wearing appropriate personal protective equipment is considered to be very low. However, HCWs who have had an occupational exposure to an MPX case in the absence of appropriate personal protective equipment should undergo active surveillance for symptoms for 21 days. Postexposure vaccination is recommended for close contacts of cases, ideally within 4 days of first exposure (and up to 14 days in the absence of symptoms), to prevent onset or mitigate disease severity. Primary preventive (preexposure) vaccination is indicated for individuals and HCWs at high risk of exposure, clinical laboratory personnel performing diagnostic testing for MPX, and outbreak response team members (as designated by national public health authorities).[3] Currently, the JYNNEOS vaccine, a third-generation vaccine approved for prevention of MPX by the US Food and Drug Administration, has been introduced and is available in Korea.

CONCLUSION

The 2022 MPX outbreak in nonendemic countries is a new threat during the ongoing COVID-19 pandemic. This outbreak presents

unique epidemiological and clinical features from those of prior outbreaks. Emergency department clinicians should be aware of clinical manifestations, evaluation, and management of MPX. In addition, to prevent transmission in healthcare settings, clinicians should understand the basics of infection control for MPX.

CONFLICT OF INTEREST

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

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Systematic Review

Effect of corticosteroid administration on cardiac arrest: a systematic review and network meta-analysis of the timing of administration

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Corticosteroids may have a beneficial effect on the outcome of cardiac arrest (CA); however, it is not known whether the timing of corticosteroid use affects the outcome. We performed a systematic review and network meta-analysis to compare the efficacy of corticosteroid administration according to the timing. A favorable final outcome, as the primary study outcome, was defined as a combination of survival with good neurologic outcome and survival for 1 year. The secondary outcome was survival to discharge. Nine clinical studies were included. Corticosteroids administered during cardiopulmonary resuscitation (CPR; odds ratio [OR], 1.29; 95% confidence interval [CI], 1.11–1.51) and post-CA (OR, 1.47; 95% CI, 1.30–1.66) had a positive effect on the favorable final outcome compared to the control protocol (no corticosteroid administration), while those used prior to CA had a negative effect. Corticosteroids administered post-CA had a positive effect on survival to discharge compared to the control protocol (OR, 1.82; 95% CI, 1.02–3.27), while those used prior to CA and during CPR had no significant effect. Post-CA was evaluated to be the best administration timing for both outcomes. In conclusion, the timing of corticosteroid administration may be an important factor for the prognosis of CA. Corticosteroids administration post-CA and during CPR may have beneficial effects on CA outcomes.

Keywords Heart arrest; Cardiopulmonary resuscitation; Adrenal cortex hormones; Steroids; Network meta-analysis

Capsule Summary

What is already known

Use of corticosteroids for the treatment of cardiac arrest may be beneficial in terms of return of spontaneous circulation, survival with good neurologic outcome, and long-term survival. However, the optimal timing for corticosteroid administration is unknown.

What is new in the current study

The timing of administration may affect the effect of corticosteroids on the prognosis of patients with cardiac arrest. Corticosteroids may be best administered after the return of spontaneous circulation regardless of whether they were administered during cardiopulmonary resuscitation or not.

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INTRODUCTION

Cardiac arrest (CA) is referred to as the abrupt loss of heart mechanical activity, as confirmed by the absence of signs of circulation. Out-of-hospital CA and in-hospital CA are important causes of mortality and morbidity worldwide, and it is estimated that 360,000 and 290,000 cases occur annually in the United States, respectively, with only 10% to 12% and 25% to 40%, respectively, of patients surviving.[1,2]

Currently, epinephrine is considered the only essential pharmaceutical therapy except for antiarrhythmic drugs in CA according to the current advanced cardiac life support (ACLS) guidelines.[3,4] Several studies have previously shown that relative adrenal insufficiency is common in patients after CA, and higher cortisol levels are associated with lower mortality from circulatory shock in animal models and humans.[5-8] These results suggest that the use of corticosteroids after CA can suppress inflammatory reactions, regulate catecholamine synthesis, and protect against ischemia-reperfusion injury.[9] Based on this concept, there have been various clinical studies that assess the effect of corticosteroid administration on CA, which showed inconsistent results.[10-18] Moreover, even the results of recent meta-analyses that included those clinical studies were inconsistent.[19-22] The designs of the clinical studies mentioned above are quite different, especially in terms of the timing of corticosteroid administration; in some cases, corticosteroids were administered during cardiopulmonary resuscitation (CPR) or after the return of spontaneous circulation (ROSC), while other patients had a history of recent corticosteroid use prior to CA. We hypothesized that this difference in timing caused the discrepancies observed in the results of existing clinical studies and meta-analyses.

We aimed to assess the effect of corticosteroid administration on CA and whether the timing of administration affects the outcome. Hence, we performed a network meta-analysis of clinical studies that assessed the effect of corticosteroid administration on CA with a head-to-head comparison of the outcomes according to the timing of corticosteroid administration and prior corticosteroid use.

METHODS

Protocol

This study followed the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) statement extension for network meta-analysis guidelines[23,24] and was prospectively registered in PROSPERO (international prospective register of systematic reviews; No. CRD42022331973).[25]

Search strategy and inclusion criteria

Two reviewers independently searched for studies published in English before May 2022 using PubMed, Embase, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials. We combined the following search words: "cardiac arrest," "heart arrest," "cardiopulmonary arrest," "cardiopulmonary resuscitation," "ventricular fibrillation," "CPR," "advanced cardiovascular life support," "ACLS," "steroid," "glucocorticoid," "hydrocortisone," "adrenal cortex hormones," "methylprednisolone," and "dexamethasone." We also searched for unpublished trials and ongoing studies at ClinicalTrials.gov (The US National Institutes of Health Ongoing Trials Register).

The studies with the following characteristics were enrolled: (1) population: adults (≥ 18 years) with CA, regardless of the CA location, with an initial presenting rhythm of CA; (2) intervention: steroid use during and/or after CA; (3) control: no steroid use (i.e., placebo or conventional ACLS therapy); (4) outcome: survival to discharge and ROSC; and (5) design: randomized controlled trial (RCTs), case-control studies, and cohort studies. In addition, the intervention group of some studies was administered additional drugs, such as vasopressin.

We excluded animal studies, case reports or series without a control group, study protocols, commentaries, review articles, and irrelevant studies (i.e., insufficient information or not in the field of interest).

Data collection and quality (risk of bias) assessment

Two reviewers independently extracted data from a data-collection form, including study title, name of author(s), publication year, country, study design, patients and demographics, interventions, timing of corticosteroid administration, and outcomes.

Risk of bias was assessed by using the Revised Cochrane risk of bias tool (RoB 2) for RCTs and GRACE (Good Research for Comparative Effectiveness) ver. 5.1 checklist for observational studies.[26,27]

Any discrepancies were resolved by discussion and consensus between two authors. In the case of a sustained disagreement, a third expert acted as a moderator.

Outcomes and intervention groups

Primary outcome was the favorable final outcome, which we defined as cerebral performance category 1 or 2 at the time of discharge or 1-year survival after CA. The secondary outcome was the survival to discharge. The timing of corticosteroid administration was categorized as administration prior to CA, during CPR, or post-CA. We classified all the cases in which corticosteroids were administered after ROSC into the post-CA group regardless of whether corticosteroids were administered during CPR or not. This was be-

cause our interest lay in whether corticosteroids were administered post-CA, when the patient is in a sepsis-like condition. Every "prior to CA" classification was based on the subject's history before the CA event in the observational study, not the timing of the actual intervention in the trial.

Statistical analysis

We calculated and presented odds ratios (ORs) with 95% confidence intervals (CIs) for each outcome and each intervention. Only the number of subjects who achieved ROSC was used as the overall count of each intervention group for the studies that enrolled whole CA patients, in order to match the conditions with those enrolled only post-CA patients. A frequentist random-effects network meta-analysis was conducted using multivariate meta-analysis and meta-regression.[28,29] The design-by-treatment model was used to confirm the consistency of the entire network.[30] The node-splitting method was also used to check the inconsistency between direct and indirect estimates of the effect.[31,32] Ranking probabilities were estimated by the surface under the cumulative ranking curve for each outcome. We used STATA ver. 17 (Stata Corp., College Station, TX, USA) for statistical calculations.

RESULTS

Study search results and characteristics

We identified 6,173 records through a database search and screened 5,018 after duplicates were removed (Fig. 1). Among these, 114 articles went through a full-text review, and 10 articles were finally selected by applying the inclusion criteria, including one case-control study,[33] five RCTs,[10-13,15] one prospective cohort study,[18] and three retrospective cohort studies (Supplementary Table 1).[14,16,17] Characteristics of the included studies are summarized in Table 1.[10-18,33]

Risk of bias in the enrolled studies

Most of the trials and all the cohort studies reviewed in the current meta-analysis were classified as those with good quality, according to RoB 2 assessment, except one trial with a high risk of bias (Supplementary Fig. 1). One case-control study was classified as a study with an uncertain risk of bias because of its lack of detailed information.[33]

Favorable final outcome

Nine studies were included for the analysis to determine the favorable final outcome.[10-13,15-18,33] The network plot of the analysis for the favorable final outcome is depicted in Fig. 2A. We did not find any inconsistency in the entire network (Supplementary Table 2). There were significant positive effects on the favorable final outcome associated with corticosteroids administered during CPR (OR, 1.29; 95% CI, 1.11–1.51) and administered post-CA (OR, 1.47; 95% CI, 1.30–1.66), compared to the control protocol (no corticosteroid administration), while there was a negative effect

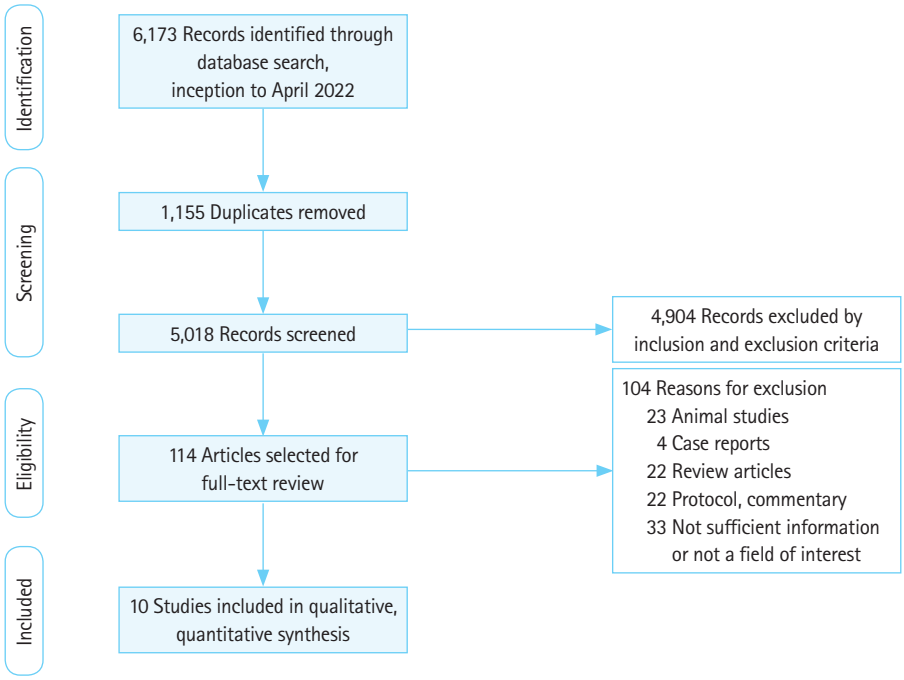

Fig. 1. PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) flowchart and study selection.

Table 1. Characteristics of the enrolled studies

Study	Design	Subject	Administration timing	Outcome				Enrolled analysis
				ROSC	GNO	SD	S1Y	
Schwitzer et al.[33] (1983)	CC	OHCA	During CPR	7	3	3	NA	SD, FFO
Paris et al.[15] (1984)	RCT	OHCA	During CPR	6	0	0	0	SD, FFO
Tsai et al.[18] (2007)	PC	OHCA	During CPR	46	1	9	NA	SD, FFO
Mentzelopoulos et al.[13] (2009)	RCT	IHCA	During CPR and post-CA	66	NA	11	NA	SD, FFO
Mentzelopoulos et al.[12] (2013)	RCT	NS	During CPR and post-CA	200	25	31	NA	SD, FFO
Bolvardi et al.[11] (2016)	RCT	NS	During CPR	15	1	NA	NA	FFO
Tsai et al.[17] (2016)	RC	NS	Prior to CA and during CPR	NA	NA	5,471	4,891	SD, FFO
Niimura et al.[14] (2017)	RC	OHCA and IHCA	Post-CA	NA	NA	253	NA	SD
Tsai et al.[16] (2019)	RC	NS	Prior to CA and post-CA	NA	NA	3,552	2,204	SD, FFO
Andersen et al.[10] (2021)	RCT	IHCA	During CPR	186	38	NA	NA	SD, FFO

ROSC, return of spontaneous circulation; GNO, good neurologic outcome; SD, survival to discharge; S1Y, 1-year survival; CC, case-control study; OHCA, out-of-hospital cardiac arrest; CPR, cardiopulmonary resuscitation; NA, not available; FFO, favorable final outcome; RCT, randomized control trial; PC: prospective cohort study; IHCA, in-hospital cardiac arrest; CA, cardiac arrest; NS, not specified; RC, retrospective cohort study.

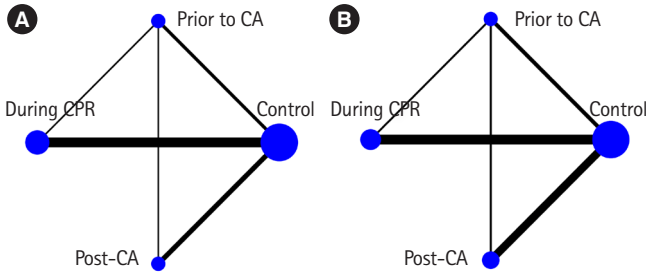

Fig. 2. Network maps of (A) the analysis for the favorable final outcome and (B) the survival to discharge. Network plot includes history of recent corticosteroid use prior to cardiac arrest (CA), corticosteroid administration during cardiopulmonary resuscitation (CPR), and corticosteroid administration post-CA.

associated with their administration prior to CA (OR, 0.70; 95% CI, 0.64–0.77). Corticosteroids administered during CPR and post-CA showed a significant positive effect on the favorable final outcome compared to that administered prior to CA (OR, 1.85; 95% CI, 1.56–2.18 and OR, 2.10; 95% CI, 1.85–2.39, respectively). Corticosteroids administration post-CA did not have a significant effect on the favorable final outcome compared to administration during CPR (OR, 1.14; 95% CI, 0.94–1.38) (Fig. 3).[10-13,15-18,33] Post-CA was shown as the best timing for corticosteroid administration to achieve a favorable final outcome with a probability of 89.9% (Table 2).

Survival to discharge

Nine studies were included for the analysis of survival to discharge.[10,12-18,33] The network plot of the analysis for the survival to discharge is depicted in Fig. 2B. We found an inconsistency in the network ($P<0.001$), and the node-splitting method detected an inconsistency between corticosteroid administration prior to CA and during CPR (Supplementary Table 3). There was a significant positive effect on survival to discharge when corticosteroids were administered post-CA compared to the control protocol (OR, 1.82; 95% CI, 1.02–3.27), while there was no significant effect associated with administration prior to CA (OR, 0.83; 95% CI, 0.45–1.55) or during CPR (OR, 1.02; 95% CI, 0.51–2.05). Corticosteroid administration post-CA showed a significant positive effect on survival to discharge compared to administration prior to CA (OR, 2.19; 95% CI, 1.04–4.63), but no significant effect of administration during CPR existed (OR, 1.23; 95% CI, 0.55–2.72). Corticosteroid administration post-CA did not have a significant effect on survival to discharge compared to administration during CPR (OR, 1.79; 95% CI, 0.72–4.47) (Fig. 4).[10,12-16,18,33] Post-CA was shown as the best timing for corticosteroid administration to achieve survival to discharge with a probability of 87.3% (Table 2).

Table 2. Ranking of the timing of corticosteroid administration

Variable	Favorable final outcome			Survival to discharge		
	SUCRA	PrBest	Mean rank	SUCRA	PrBest	Mean rank
Placebo	33.3	0	3.0	40.1	0.9	2.8
Prior to CA	0	0	4.0	20.2	1.1	3.4
During CPR	70.0	10.1	1.9	44.8	10.7	2.7
Post-CA	96.6	89.9	1.1	94.9	87.3	1.2

SUCRA, surface under the cumulative ranking curve; PrBest, probability for the best timing; CA, cardiac arrest; CPR, cardiopulmonary resuscitation.

DISCUSSION

To the best of our knowledge, this was the first network meta-analysis ever performed regarding the effect of corticosteroid administration on CA. The results of our current network meta-analysis suggest that the timing of corticosteroid administration may

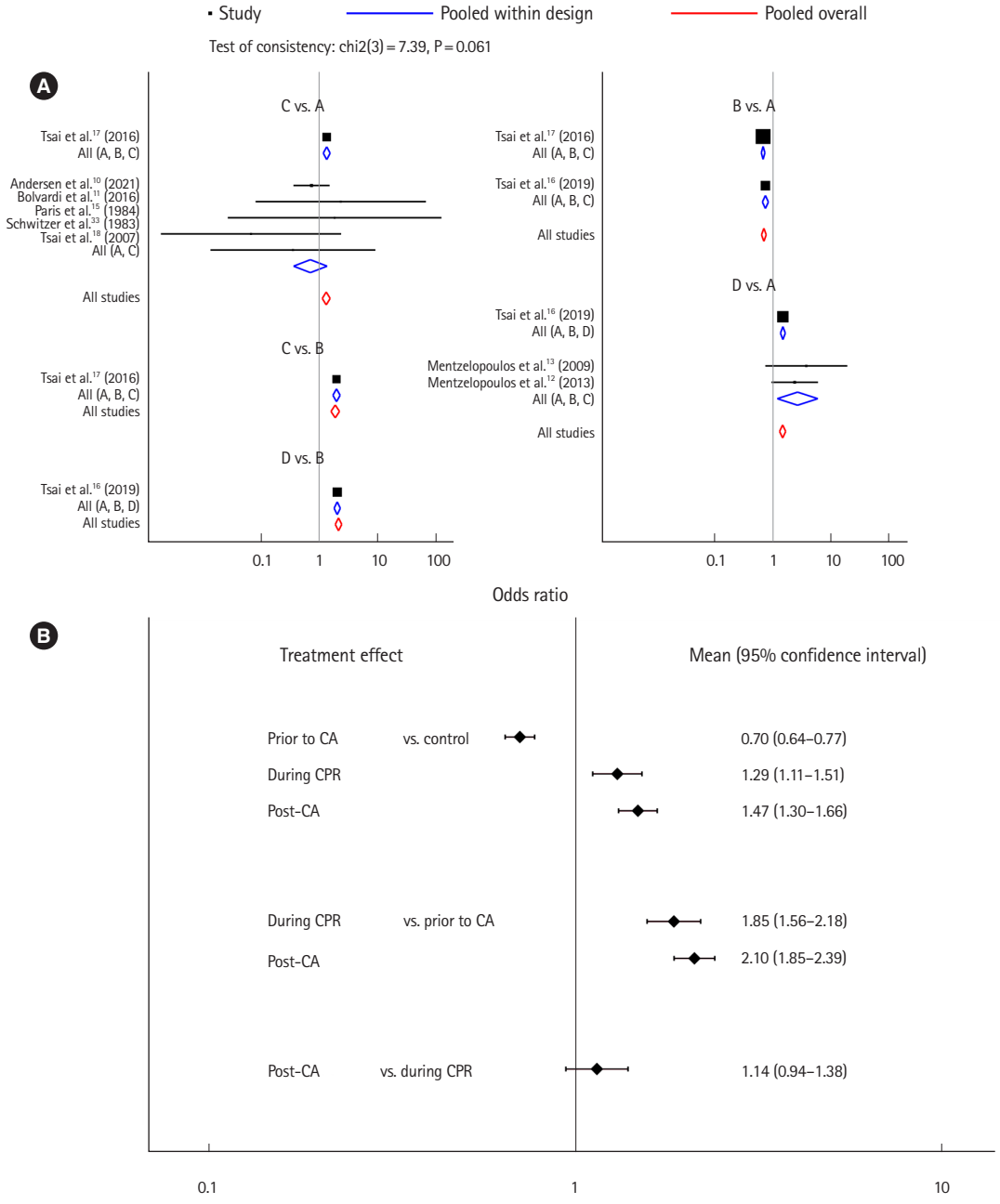

Fig. 3. The analysis for the favorable final outcome. (A) Forest plot and (B) interval plot. In treatment arm: A, control; B, history of recent corticosteroid use prior to cardiac arrest (CA); C, corticosteroid administration during cardiopulmonary resuscitation (CPR); and D, corticosteroid administration post-CA.

affect the outcome of CA patients. They also suggest that the discrepancy among the results of previous clinical studies assessing the effect of corticosteroid administration on CA may be due to differences in the study setting regarding the timing of administration. We can assume that the discrepancy among the meta-analyses that enrolled those studies could be due to differences in the setting of enrolled studies in each meta-analysis.

CA is a devastating medical condition that leads to high socio-economic costs from which only a small portion of patients can achieve meaningful recovery. Its poor prognosis results from global cerebral ischemia-reperfusion injury, systemic inflammatory response, activation of the apoptotic pathway, free radical production, and myocardial injury.[34-37] It also causes disorders of the immune system and hemodynamic instability with increased levels of endotoxins and cytokines, i.e., a so-called sepsis-like syndrome.[34] One study showed that the serum cortisol level was de-

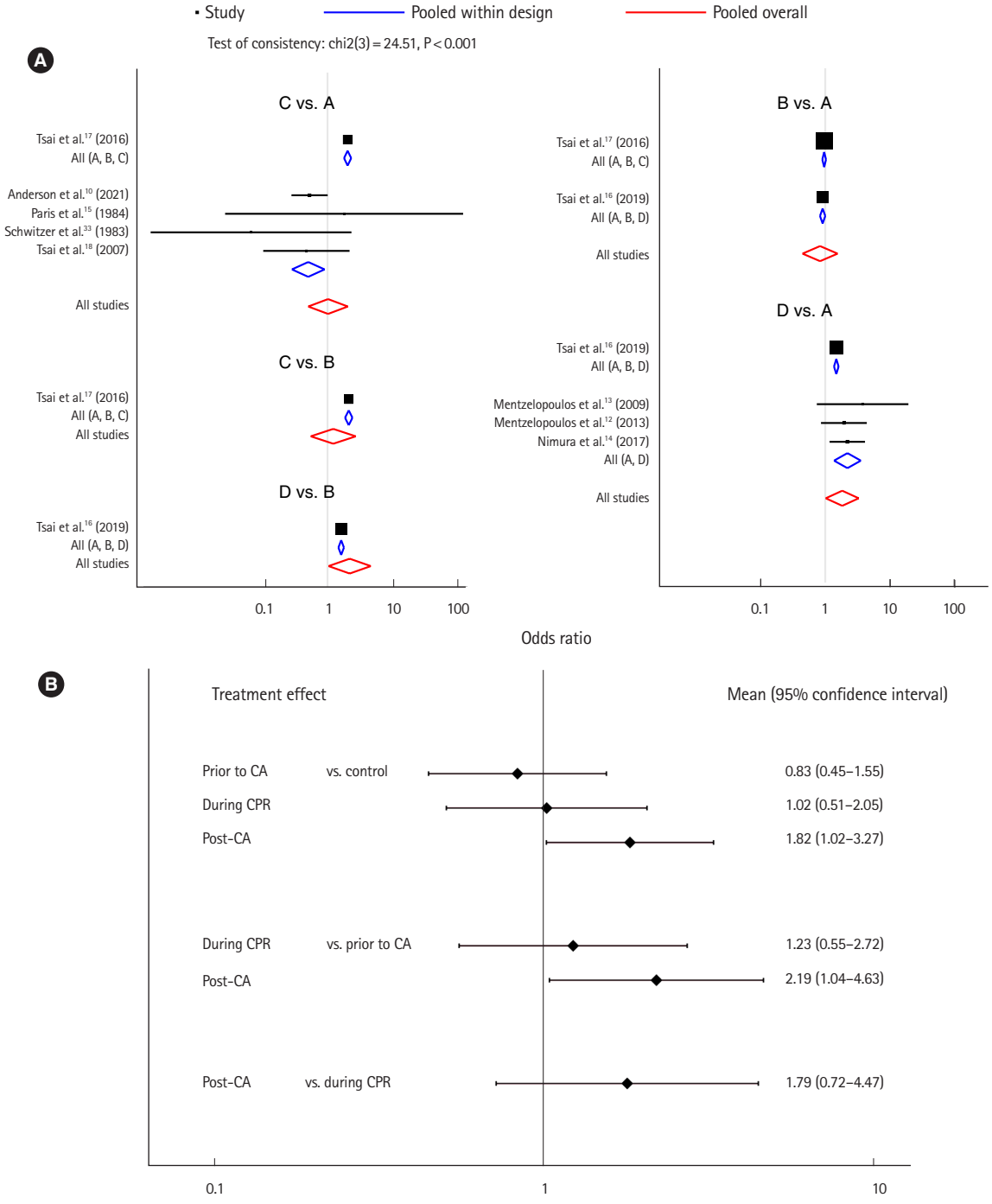

Fig. 4. The analysis for survival to discharge. (A) Forest plot and (B) interval plot. In treatment arm: A, control; B, history of recent corticosteroid use prior to cardiac arrest (CA); C, corticosteroid administration during cardiopulmonary resuscitation (CPR); and D, corticosteroid administration post-CA.

creased after ROSC and was associated with short-term survival.[38] These results initiated studies evaluating the effect of corticosteroid administration on CA. As a result, it was known that corticosteroid administration in CA improves cardiovascular stability through control of the systemic inflammatory response and improvement of the vascular response to vasopressors by lowering the catecholamine reuptake; it also helps to reduce myocardial and cerebral injury by reducing oxidative stress.[39-43]

Many clinical studies that assessed the effect of corticosteroids on CA showed inconsistent results; therefore, the use of corticosteroids for the treatment of CA is recommended in a limited fashion with uncertain value in current guidelines for CPR.[3] Our current

study suggests that the timing of administration may be an important factor in the effect of corticosteroids on CA. Based on this, further research directly comparing the effects on CA according to the timing of corticosteroid administration is necessary to establish a clinical guideline for corticosteroid use during CA treatment.

One of the most interesting findings in our research was that the outcomes of CA were significantly worse in patients to whom corticosteroids were administered prior to CA compared to controls; otherwise, the outcomes were significantly better than control group outcomes if corticosteroids were administered during CPR or post-CA. Considering that patients administered corticosteroids prior to CA, when included in our network meta-analysis, included those in whom a history of corticosteroid administration was identified during a short-term period before the CA event, it is likely that this group included chronic corticosteroid users. Adrenal insufficiency associated with chronic corticosteroid use may explain the worse prognosis in this group.[44] However, this result would better be accepted as a phenomenon showing that the prognosis is worse than that of the control group in a situation where relative adrenal insufficiency is suspected rather than as a recommendation for the timing of administration, considering that the "prior to CA" classification in original studies was not based on an actual timing of intervention but instead was a result of retrospective observation.

The results of our study also suggest that the effect of corticosteroids on CA may be better when they are administered after CA than when administered during CPR. We failed to identify a statistically significant difference in the indirect comparison of the effects of corticosteroids administered during CPR and those administered after CA, although there were consistent tendencies showing a relative superiority of their administration after CA. However, the results of the ranking probability tests for both outcomes support the better effect of corticosteroid administration after CA. Moreover, corticosteroid administration during CPR did not even show a significant difference in the comparison with the control protocol for survival to discharge. Considering the sepsis-like condition of post-CA patients, timely administration of corticosteroids targeting this condition may explain the better effect. Recent studies showing that corticosteroid administration after cerebral ischemia-reperfusion reduces neurological damage through the inhibition of apoptosis and inflammatory responses may also support this finding.[45,46]

The results of the inconsistency test using the design-by-treatment model showed that the analysis of the primary outcome met the assumptions about consistency and homogeneity to some extent.[28] Therefore, it showed that our result from the analysis for the favorable final outcome could be reliable. On the other hand, the result of the analysis for survival to discharge, the secondary outcome, which did not meet those assumptions, may be difficult to accept. However, it could be adopted as a supportive result for the analysis of the favorable final outcome, considering that the results of both analyses showed a similar trend.

Our network meta-analysis had a few limitations. First, we used a newly defined outcome measure, the favorable final outcome, as a primary outcome, instead of a widely used one, such as survival with good neurologic recovery. This was because information regarding neurologic recovery was not available in two studies with the largest effect sizes.[16,17] Those studies used 1-year survival as an outcome measure reflecting long-term prognosis. Hence, we had to define a new outcome measure that can reflect the ultimate prognosis as much as possible, which was a combination of survival with good neurologic function and 1-year survival. Second, the design and quality of the studies included in our analysis vary compared to their number, and this may compromise the consistency and homogeneity, which are important for the reliability of a network meta-analysis. Hence, caution in adopting the results of our study despite our efforts to overcome this limitation, such as the use of design-by-treatment model or publication bias assessment, should be taken. Third, the analysis for the secondary outcome, survival to discharge, did not meet the consistency assumption of a network meta-analysis. Hence, one should be careful to adopt the result of the analysis for survival to discharge, especially for the comparison between corticosteroids administered prior to CA and those administered during CPR, which showed inconsistency. Fourth, we also classified studies with co-administered drugs such as vasopressin into the corticosteroid administration group, as in most of the prior pairwise meta-analyses dealing with the effect of corticosteroids on CA[19,21,22]; therefore, the possibility of errors due to differences in the intervention regimen cannot be excluded. Hence, caution is required in adopting our results because there might be an interaction of co-administered drugs that affects the efficacy of corticosteroids on CA. Fifth, our post-CA classification included cases of corticosteroid administration during CPR as well as after ROSC. Therefore, we could not rule out the possibility that our results, which showed that post-CA could be a better timing of corticosteroid administration, were attributable to the effect of repeated administration. Finally, our results did not contain enough direct comparisons for checking inconsistencies. Further research to directly compare the effects of corticosteroid administration according to the timing of administration is necessary.

In conclusion, the timing of corticosteroid administration may be an important factor for the prognosis of CA. Corticosteroids administration post-CA and during CPR may have beneficial ef-

fects on the outcomes of CA compared to the control protocol. Corticosteroids administration post-CA may have better efficacy than administration during CPR. Also, our data suggest that corticosteroid use prior to CA may be associated with poor outcomes.

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Search strategy
Supplementary Table 2. Pairwise and loop inconsistency estimates of the analysis for the favorable final outcome
Supplementary Table 3. Pairwise and loop inconsistency estimates of the analysis for the survival to discharge
Supplementary Fig. 1. Risk of bias assessments.
Supplementary materials are available at https://doi.org/10.15441/ceem.22.371.

CONFLICT OF INTEREST

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

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AUTHOR CONTRIBUTIONS

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Original Article

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Comparison of intracranial pressure changes in out-of-hospital cardiac arrest patients with and without malignant blood-brain barrier disruption

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Objective In the present study, intracranial pressure (ICP) changes were investigated in out-of-hospital cardiac arrest (OHCA) patients with and without malignant blood-brain barrier (BBB) disruption who underwent target temperature management.

Methods This prospective, single-center, observational study was conducted from June 2019 to December 2021. ICP and albumin quotient values were measured on days 1, 2, 3, and 4 of hospitalization. Malignant BBB disruption was defined as the sum of scores for the degree of BBB disruption ≥ 9 on days 1 to 4.

Results ICP in OHCA patients without malignant BBB disruption on days 1, 2, 3, and 4 of hospitalization was 9.58 ± 0.53, 12.32 ± 0.65, 14.39 ± 0.76, and 13.88 ± 0.87 mmHg, respectively, and in OHCA patients with malignant BBB disruption 13.65 ± 0.74, 15.72 ± 0.67, 16.10 ± 0.92, and 15.22 ± 0.87 mmHg, respectively ($P < 0.001$, $P < 0.001$, $P = 0.150$, and $P = 0.280$, respectively). The P-values of changes in ICP between days 1 and 2, days 2 and 3, and days 3 and 4 of hospitalization in OHCA patients without malignant BBB disruption were $P < 0.001$, $P = 0.001$, and $P = 0.540$, respectively, and in OHCA patients with malignant BBB disruption were $P = 0.002$, $P = 0.550$, and $P = 0.100$, respectively.

Conclusion Among OHCA patients treated with target temperature management, ICP was higher on days 1 and 2 of hospitalization and an increase in ICP occurred earlier with malignant BBB disruption than without malignant BBB disruption.

Keywords Intracranial pressure; Out-of-hospital cardiac arrest; Blood-brain barrier; Induced hypothermia

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Capsule Summary

What is already known

Ischemia-reperfusion brain injury following out-of-hospital cardiac arrest (OHCA) due to oxidative stress, intracellular calcium influx, and glutamate production cause blood-brain barrier (BBB) disruption, resulting in brain edema and increased intracranial pressure (ICP).

What is new in the current study

Although ICP was within the normal range following OHCA regardless of malignant BBB disruption, the increase in ICP in the OHCA patients with malignant BBB disruption was higher and earlier than in OHCA patients without malignant BBB disruption.

INTRODUCTION

The blood-brain barrier (BBB) regulates the entry of substances in plasma into the brain and is composed of microvascular endothelial cells, a capillary basement membrane, pericytes, and astrocyte endfeet. Endothelial cells form junctional complexes with tight junctions and adherens junctions.[1-3] BBB disruption can occur in Alzheimer's disease, infection, traumatic brain injury, stroke, cancer, and epilepsy.[4-7] Neurotoxic materials in the plasma enter the central nervous system through the disrupted BBB and cause neuronal injuries.[8,9]

Hypoxic ischemic brain injury after cardiac arrest (CA) increases the BBB permeability due to microvascular damage induced by oxidative stress, resulting in BBB disruption.[10] In cytotoxic edema, the total brain tissue mass remains unchanged; however, in vasogenic edema resulting from BBB disruption, water is added from the vascular space, which leads to tissue swelling, tissue movement, and, eventually, elevated intracranial pressure (ICP).[11,12] Cerebral edema and elevated ICP lead to reduced cerebral blood flow, resulting in a vicious cycle of cerebral injury due to decreased cerebral blood flow.[13-16]

In previous studies, moderate or severe BBB disruption was strongly associated with poor neurological outcomes, and a BBB disruption score ≥ 9 had poor neurological outcomes in survivors of out-of-hospital CA (OHCA) who had undergone target temperature management (TTM).[17,18] Sekhon et al.[19] reported a relatively low burden of ICP, however, most CA patients demonstrated an increased compensatory reserve index, indicating a state of limited intracranial compensatory reserve and compliance in hypoxic ischemic brain injury after CA.

To the best of our knowledge, ICP with BBB disruption scores ≥ 9 (defined as malignant BBB disruption) has not yet been investigated. Therefore, ICP changes in OHCA patients with and without malignant BBB disruption who underwent TTM were investigated in the present study. The results can be used as baseline ICP data in future studies aimed at diminishing malignant BBB disruption.

METHODS

Ethical statements

This study was approved by the Institutional Review Board of Chungnam National University Hospital (No. CNUH IRB 2019-07-033-09). All procedures and protocols were conducted in accordance with the Declaration of Helsinki and the International Conference of Harmonisation Good Clinical Practice and reported as CONSORT (Consolidated Standards of Reporting Trials) criteria. Approval and written informed consent from the patients' next of kin were obtained prior to study enrollment. The research method used in previous studies was followed in the present study.[20,21]

Study design and patients

This study was a single-center, prospective, observational cohort study of OHCA patients treated with TTM between June 2019 and December 2021. For the primary endpoint, ICP changes in OHCA patients with and without malignant BBB disruption who underwent TTM were investigated. The patients' caregivers were called 6 months after the return of spontaneous circulation (ROSC) to obtain patient neurological outcome data. A cerebral performance category (CPC) of 1 to 2 demonstrated good neurologic outcomes and a CPC of 3 to 5 was associated with poor neurologic outcomes. Resuscitated OHCA patients who were treated with TTM and whose Glasgow Coma Scale (GCS) score was ≤ 8 after ROSC were included in this study. The exclusion criteria were as follows: (1) < 18 years of age, (2) CA due to trauma or TTM interruption due to hemodynamic instability, (3) ineligibility for TTM (i.e., brain hemorrhage, active bleeding, known terminal illness, or poor neurological status before CA), (4) ineli-

gibility for lumbar puncture (i.e., severe cerebral edema on brain computed tomography, loss of the basal cisterns, intracranial mass, antiplatelet therapy, anticoagulation therapy, or coagulopathy; platelet count $< 40 \times 10^3$/mL or international normalized ratio > 1.5),[22] (5) receiving extracorporeal membrane oxygenation, (6) refusal of lumbar puncture by the kin, and (7) cases in which the next of kin refused further treatment.

TTM protocol

TTM was performed using cooling devices (Arctic Sun Energy Transfer Pads; Medivance Inc., Louisville, CO, USA). The target temperature of 33°C was maintained for 24 hours with subsequent rewarming to 37°C at a rate of 0.25°C/hr, and the temperature was monitored using esophageal and bladder temperature probes. Midazolam (0.05 mg/kg intravenous bolus, followed by a titrated intravenous continuous infusion at a dose between 0.05 and 0.2 mg/kg/hr) and cisatracurium (0.15 mg/kg intravenous bolus, followed by an infusion up to 0.3 mg/kg/hr) were used for shivering control and sedation, and anesthesia depth was monitored using the Anesthetic Depth Monitor for Sedation (Unimedics Co., Seoul, Korea). Electroencephalography was performed for persistent deterioration of the patient's level of consciousness, involuntary movements, or seizures. Patients with electrographic seizures or clinically diagnosed seizures were treated with antiepileptic drugs (levetiracetam; loading dose: a 2-g bolus intravenously, maintenance dose: a 1-g bolus intravenously twice daily). Fluids or vasopressors were administered when necessary to maintain the mean arterial pressure between 85 and 100 mmHg.[23]

Data collection

The following data were collected: age, sex, CA witness, bystander cardiopulmonary resuscitation (CPR), first monitored cardiac rhythm, etiology of CA, time from ROSC to reaching the target temperature of 33°C (induction time), time from ROSC to measuring ICP via lumbar puncture (ICP time), time from collapse to CPR (no flow time), time from CPR to ROSC (low flow time), sequential organ failure assessment, GCS scores after ROSC, and CPC at 6 months after ROSC.

Measurement of ICP and Qa

The ICP was measured after the patient was placed in the lateral decubitus position and a lumbar catheter inserted using a Hermetic lumbar accessory kit (Integra Neurosciences, Plainsboro, NJ, USA) at the level between the third and fourth lumbar vertebrae of the patient with hip and knee flexed.[24] ICP was continuously measured using a LiquoGuard pump system (Möller-Medical, Fulda, Germany) and taken as the average of the values measured for 1 hour before obtaining cerebrospinal fluid (CSF). Serum blood samples were obtained via venipuncture. Serum and CSF samples were obtained on the first day of hospitalization and on every subsequent day of hospitalization as follows: CSF serum albumin quotient (Qa) values were calculated on days 1 (Qa_1), 2 (Qa_2), 3 (Qa_3), and 4 (Qa_4) of hospitalization. BBB disruption was defined as normal (Qa, ≤ 0.007), mild (Qa, 0.007 to 0.01), moderate (Qa, 0.01 to 0.02), or severe (Qa, ≥ 0.02).[25] Based on a previous study, malignant BBB disruption was defined when the sum of the scores for the weighted degree of BBB disruption was ≥ 9 on days 1 to 4 (for example, 0^2 [normal, day 1]+1^2 [mild, day 2]+2^2 [moderate, day 3]+3^2 [severe, day 4] = 14).[18]

Statistical analysis

Continuous variables were described as medians with interquartile ranges or means and standard deviations depending on the normal distribution. Categorical variables were described as frequencies and percentages. The two groups were compared using the chi-square test and Fisher exact test. The correlation between Qa, and ICP was analyzed using Kendall's tau. The changes in ICP levels over time were analyzed using the generalized estimating equation and Bonferroni post hoc test based on the presence or absence of malignant BBB disruption. All statistical analyses were performed using PASW SPSS ver. 18.0 (SPSS Inc., Chicago, IL, USA) and MedCalc ver. 15.2.2 (MedCalc Software, Ostend, Belgium). Results were considered statistically significant when the P-value was less than 0.05.

RESULTS

Characteristics of study subjects

Among the 148 OHCA patients in whom ROSC was recorded, 62 patients were enrolled in this study: 26 patients without malignant BBB disruption and 36 with malignant BBB disruption (Fig. 1). In the patients without malignant BBB disruption, 21 subjects (80.8%) had good neurological outcomes, and in the patients with malignant BBB disruption, seven (19.5%) had good neurological outcomes. Furthermore, 23 patients underwent delayed percutaneous coronary intervention for the evaluation of acute myocardial infarction as the cause of OHCA after TTM in the present study. Differences were not observed between the core temperature measured using an esophageal or bladder temperature probe. Complications associated with the lumbar drainage catheter, including bleeding, infection, or brain herniation, did not occur in the enrolled patients. Significant differences were not observed between the patients with and without malignant BBB

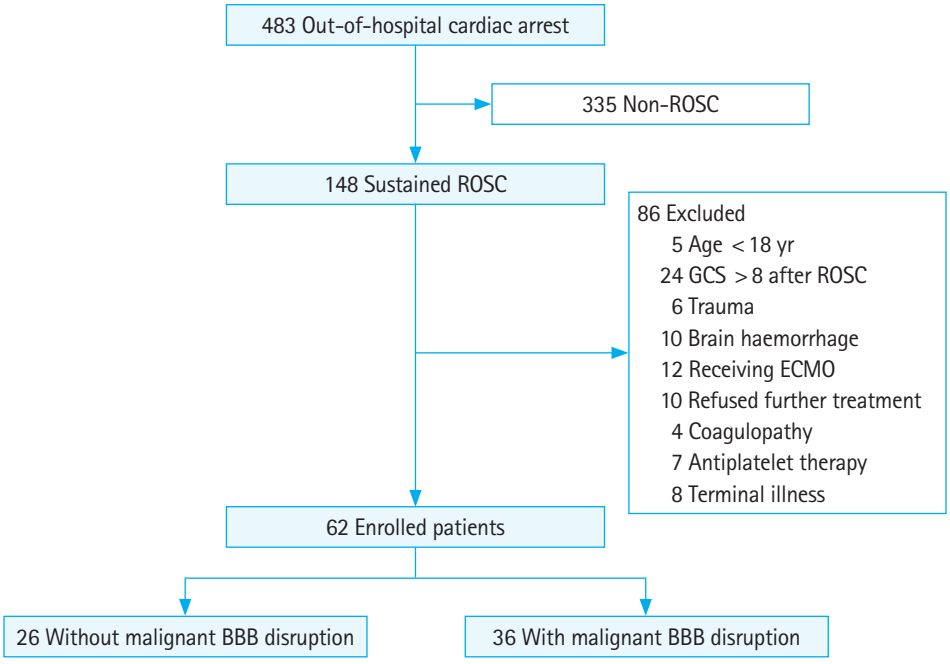

Fig. 1. Flow chart of the study. ROSC, return of spontaneous circulation; GCS, Glasgow Coma Score; ECMO, extracorporeal membrane oxygenation; BBB, blood-brain barrier.

disruption in terms of mean age, sex, presence of a witness, bystander CPR, cardiac etiology, ICP time, induction time, no flow time, and sequential organ failure assessment scores (Table 1). Among the 62 enrolled patients, 22 (35.5%), 6 (9.7%), 1 (1.6%), 20 (32.3%), and 13 (21.0%) had a CPC of 1, 2, 3, 4, and 5, respectively. A CPC of 5 was observed in 13 patients (21.0%) with conservative management after completion of TTM. Among the 62 enrolled patients, 10 patients died after organ donation and five died of pneumonia.

Correlation of ICP and Qa in patients with and without malignant BBB disruption

Overall, correlation coefficients between Qa and ICP were 0.62 (95% confidence interval [CI], -0.30 to 0.47), 0.14 (95% CI, -0.16 to 0.45), 0.19 (95% CI, -0.19 to 0.49), and 0.26 (95% CI, -0.14 to 0.54) on days 1, 2, 3, and 4 of hospitalization, respectively. In the OHCA patients without malignant BBB disruption, correlation coefficients between Qa and ICP were 0.55 (95% CI, -0.39 to 1.00), -0.05 (95% CI, -0.41 to 1.00), 0.68 (95% CI, -0.15 to 0.40), and 0.43 (95% CI, -0.56 to 1.00) on days 1, 2, 3, and 4 of hospitalization, respectively. In the OHCA patients with malignant BBB disruption, correlation coefficients between Qa and ICP were -0.22 (95% CI, -0.54 to 0.21), -0.01 (95% CI, -0.37 to 0.34), -0.05 (95% CI, -0.44 to 0.37), and 0.07 (95% CI, -0.51 to 0.59) on days 1, 2, 3, and 4 of hospitalization, respectively.

Comparison of ICP between the patients with and without malignant BBB disruption

On days 1 and 2 of hospitalization, ICP was higher in the patients with malignant BBB disruption than in the patients without malignant BBB disruption, however, on days 3 and 4 of hospitalization, ICP was similar in both patient groups (Table 2 and Fig. 2).

Comparison of daily ICP changes in the OHCA patients with and without malignant BBB disruption

In the patients without malignant BBB disruption, significant changes were observed in ICP between days 1, 2, and 3 of hospitalization. In the patients with malignant BBB disruption, significant changes were observed in ICP between days 1 and 2 of hospitalization (Table 3).

DISCUSSION

In the present study, differences were observed in the incidence of shockable rhythm at the time of CA, low flow time, and GCS immediately after ROSC between the OHCA patients with and without malignant BBB disruption. ICP in the patients with malignant BBB disruption was significantly higher than in the patients without malignant BBB disruption on days 1 and 2 of hospitalization, although the average ICP in OHCA patients treated with TTM was between 9.58 and 16.10 mmHg at any time point in both patient groups. A different pattern was observed with a

Table 1. General characteristics (n=62)

Characteristic	Total	Without malignant BBB disruption (n=26)	With malignant BBB disruption (n=36)	P-value
Age (yr)	54.16±17.17	49.46±17.44	57.56±16.38	0.070
Sex				0.440
Male	47 (75.8)	21 (80.8)	26 (72.2)	
Female	15 (24.2)	5 (19.2)	10 (27.8)	
Witness				0.160
Yes	34 (54.8)	17 (65.4)	17 (47.2)	
No	28 (45.2)	9 (34.6)	19 (52.8)	
Bystander CPR				0.060
Yes	42 (67.7)	21 (80.8)	21 (58.3)	
No	20 (32.3)	5 (19.2)	15 (41.7)	
Shockable rhythm				0.001
Yes	19 (30.6)	14 (53.8)	5 (13.9)	
No	43 (69.4)	12 (46.2)	31 (86.1)	
Cardiac etiology				0.210
Yes	23 (37.1)	12 (46.2)	11 (30.6)	
No	39 (62.9)	14 (53.8)	25 (69.4)	
Glasgow Coma Scale				0.010
3	52 (83.9)	16 (61.5)	36 (100)	
4	3 (4.8)	3 (11.5)	0 (0)	
5	3 (4.8)	3 (11.5)	0 (0)	
6	1 (1.6)	1 (3.8)	0 (0)	
7	1 (1.6)	1 (3.8)	0 (0)	
8	2 (3.2)	2 (7.7)	0 (0)	
Neurologic outcome				<0.001
Good	28 (45.2)	21 (75.0)	7 (25.0)	
Poor	34 (54.8)	5 (14.7)	29 (85.3)	
Induction to TTM time (hr)	5.99±3.04	6.34±2.83	5.74±3.20	0.450
No flow time (min)	2.00 (0.00–13.75)	1.00 (0.00–5.00)	4.00 (1.00–14.00)	0.640
Low flow time (min)	19.00 (9.50–29.50)	15.00 (8.00–22.00)	25.00 (14.00–40.00)	0.003
ICP measurement time (hr)	4.37 (3.22–6.00)	4.53 (3.23–6.16)	4.35 (3.00–6.00)	0.480
SOFA score	10.00 (8.00–11.25)	9.00 (7.75–10.25)	10.50 (9.00–12.00)	0.060

Values are presented as number (%) for categorical variables and mean±standard deviation or median (interquartile range) for continuous variables depending on normal distribution.
BBB, blood-brain barrier; CPR, cardiopulmonary resuscitation; TTM, target temperature management; ICP, intracranial pressure; SOFA, sequential organ failure assessment.

Table 2. Comparison of ICP between groups with and without malignant BBB disruption

Day	ICP in group without malignant BBB disruption (mmHg)	ICP in group with malignant BBB disruption (mmHg)	P-value
1	9.58±0.53	13.65±0.74	<0.001
2	12.32±0.65	15.72±0.67	<0.001
3	14.39±0.76	16.10±0.92	0.150
4	13.88±0.87	15.22±0.87	0.280

Values are presented as estimated mean±standard error.
ICP, intracranial pressure; BBB, blood-brain barrier.

Table 3. Comparison of daily intracranial pressure changes in groups with and without malignant BBB disruption

Group	P_{GEE}	Bonferroni post hoc analysis		
		Day 1–2	Day 2–3	Day 3–4
Without malignant BBB disruption	<0.001	<0.001	0.001	0.540
With malignant BBB disruption	<0.001	0.002	0.550	0.100

BBB, blood-brain barrier; P_{GEE}, P-value of generalized estimating equation.

statistically significant increase in ICP until day 2 of hospitalization in the patients with malignant BBB disruption; however, an increase in ICP in the patients without malignant BBB disruption was not observed until day 3 of hospitalization, and the ICP in both patient groups became similar after day 3 of hospitalization.

The BBB plays an important role in maintaining optimal brain function by regulating the interstitial fluid microenvironment. BBB disruption leads to its failure to sufficiently block the trans-

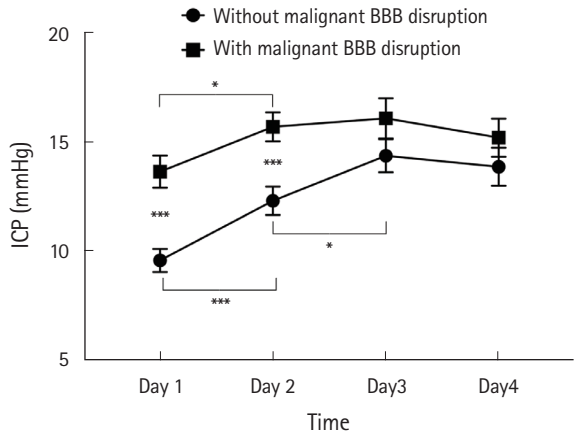

Fig. 2. Intracranial pressure (ICP) over time in out-of-hospital cardiac arrest patients with and without malignant blood-brain barrier (BBB) disruption on days 1, 2, 3, and 4 of hospitalization. On days 1 and 2 of hospitalization, significant changes were observed in ICP in the patients with malignant BBB disruption; however, significant changes were observed in ICP between days 1, 2, and 3 of hospitalization in the patients without malignant BBB disruption. In addition, ICP was higher in the patients with malignant BBB disruption than in the patients without malignant BBB disruption on days 1 and 2 of hospitalization. *P<0.05; ***P<0.001.

port of neurotoxins to the central nervous system, resulting in cerebral edema.[26-28] When moderate or severe BBB disruption occurs, the probability of poor neurological outcomes is higher than good neurological outcomes.[18] To evaluate the degree of BBB disruption, several methods have been used, such as dynamic contrast-enhanced magnetic resonance imaging, S100B protein, and Qa.[29,30]

Among these methods, Qa is a reliable method for the functional assessment of BBB disruption and commonly used in routine clinical practice and research.[31,32] In particular, the BBB disruption score using Qa is a valuable predictor of neurological prognosis in OHCA patients treated with TTM, and the area under the receiver operating characteristic curve of BBB disruption score cutoff value of 9 for poor neurological outcomes was 0.94.[18] In the present study, a BBB disruption score cutoff value ≥9 was defined as malignant BBB disruption, and 80.5% of OHCA patients with malignant BBB disruption had poor neurological outcomes.

The disruption of the BBB under ischemic conditions is multifactorial and may involve factors such as enhanced production of inflammatory cytokines, excessive oxidative stress, and upregulation of vascular endothelial growth factors.[33,34] An increase in BBB permeability allows extravasation of albumin and other high molecular weight compounds into the extracellular compartment of the brain, resulting in vasogenic edema and subsequent cell injury. Increase in BBB permeability and formation of cerebral edema may lead to increased ICP.[35-37] However, in a previous study, ICP was within the normal range in both patient groups, although the ICP in the poor neurological outcome group was higher than in the good neurological outcome group.[21]

TTM reduces reperfusion injury by modulating the following mechanisms: production of free oxygen radicals, excitotoxic neurotransmitter release, and calcium influx. In addition, TTM reduces the cerebral metabolic rate and prevents mitochondrial breakdown and cellular apoptosis. Finally, TTM lowers the ICP by preventing BBB disruption and reducing brain edema.[38,39] In the present study, ICP in OHCA patients treated with TTM was within the normal range, and statistically significant correlations were not found between Qa and ICP in both OHCA patients with and without malignant BBB disruption, although ICP in the subjects with malignant BBB disruption was higher than in the patients without malignant BBB disruption on days 1 and 2 of hospitalization.

The present study had several limitations. First, this was a single-center study with a small sample size, which might limit the generalizability of our findings. Second, CSF albumin levels were measured in CSF obtained using a lumbar catheter. In a previous study, the albumin concentration in the lumbar space was reportedly 2.2 times higher than in the ventricle.[40] Third, other biomarkers, such as neurofilament light chain, were not measured; therefore, we could not speculate on the changes in these parameters. Finally, the investigator was not blinded throughout the experiment. Future studies involving blinding are needed to address this limitation.

In conclusion, among OHCA patients treated with TTM, ICP was higher on days 1 and 2 of hospitalization and the increase in ICP occurred earlier in OHCA patients with malignant BBB disruption than in OHCA patients without malignant BBB disruption. However, the average ICP ranged from 9.58 to 16.10 mmHg at any time point in both patient groups.

CONFLICT OF INTEREST

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

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AUTHOR CONTRIBUTIONS

Conceptualization: SL, YY; Data curation: CK, HJA, JSP; Formal

analysis: CK, HJA, JSP; Methodology: SL, YY; Visualization: SL, WJ; Writing–original draft: SL, WJ; Writing–review & editing: JHM, YNI. All authors read and approved the final manuscript.

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Original Article

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Machine learning for the prediction of preclinical airway management in injured patients: a registry-based trial

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Objective The aim of this study was to determine the feasibility of using machine learning to establish the need for preclinical airway management for injured patients based on a standardized emergency dataset.

Methods A registry-based, retrospective analysis was conducted of adult trauma patients who were treated by physician-staffed emergency medical services in southwestern Germany between 2018 and 2020. The primary outcome was to assess the feasibility of using the random forest (RF) and Naive Bayes (NB) machine learning algorithms to predict the need for preclinical airway management. The secondary outcome was to use a principal component analysis to determine the attributes that can be used and advanced for future model development.

Results In total, 25,556 adults with multiple injuries were identified, including 1,451 patients (5.7%) who required airway management. Key attributes were auscultation, injury pattern, oxygen therapy, thoracic drainage, noninvasive ventilation, catecholamines, pelvic sling, colloid infusion, initial vital signs, preemergency status, and shock index. The area under the receiver operating characteristics curve was between 0.96 (RF; 95% confidence interval [CI], 0.96–0.97) and 0.93 (NB; 95% CI, 0.92–0.93; $P<0.01$). For the prediction of airway management, RF yielded a higher precision-recall area than NB (0.83 [95% CI, 0.8–0.85] vs. 0.66 [95% CI, 0.61–0.72], respectively; $P<0.01$).

Conclusion To predict the need for preclinical airway management in injured patients, attributes that are commonly recorded in standardized datasets can be used with machine learning. In future models, the RF algorithm could be used because it has robust prediction accuracy.

Keywords Intratracheal intubation; Machine learning; Bayes theorem; Wounds and injuries; Decision trees

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Capsule Summary

What is already known

Preclinical airway management is a high risk procedure. Other than a Glascow Coma Scale of less than 9 or acute respiratory insufficiency, there are few methods to predict the need for preclinical airway management.

What is new in the current study

We developed and validated a machine learning model to predict the need for airway management in injured patients.

INTRODUCTION

International guidelines recommend preclinical airway management as a potential life-saving procedure for severely injured patients with traumatic brain injury and a Glasgow Coma Scale (GCS) <9; severe respiratory insufficiency, for example, due to thoracic trauma or airway injuries; or trauma-associated shock.[1-3] However, preclinical airway management is a high-risk procedure due to imminent hypoxia, challenging environmental conditions, and varying clinician experience in managing difficult airway situations.[4,5] Because hemodynamic conditions and the patient's state of awareness can change quickly, preclinical trauma care is a highly dynamic situation. Therefore, an ability to predict or exclude the need for airway management would assist decision-making.

In recent years, several machine learning models that can predict the need for endotracheal intubation in intensive care patients have been published. They are based on electronic medical record systems and common clinical hemodynamic and laboratory parameters.[6-9] In preclinical trauma medicine, no such model exists.

German emergency medical services are divided into paramedic and emergency physician systems (grounded or air), which are alarmed by the rescue coordination center in parallel or sequentially depending on the emergency. Certain medical interventions, such as drug therapy or airway management, are restricted by law to emergency physicians except when needed for resuscitation or when an emergency physician is unavailable. German emergency physicians recruit themselves mainly from fields such as anesthesiology, internal medicine, and surgery. The specialization can be achieved in parallel with main medical specialist training after two years of clinical practice, which must contain at least a 6-month rotation in the accident and emergency department or intensive care unit.[5,10] For quality improvement, the German state of Baden-Wuerttemberg (population, 11.1 million in 2020; area, 35,751 km^2; capital, Stuttgart) created a Center for Quality Management in Emergency Medical Services in 2011. Since then, all paramedics and preclinical emergency physicians have had to provide anonymous, digital documentation to the minimal emergency dataset (MIND).[10,11] The MIND has the advantage of being used throughout Germany, and it also contains international standardized examination findings, diagnoses, and interventions that are used in the German Trauma Registry and the German Resuscitation Registry. Divided into subcategories according to the Advanced Trauma Life Support (ABCDE) algorithm at first contact and hospital admission and supplemented by a free text anamnesis and history (including vital signs diagram) of pharmaceutical therapy and medical interventions, the MIND provides nationwide, standardized, emergency documentation. Although the free text and history sections are not available digitally, the MIND seems suitable for research with machine learning.

Therefore, the aim of this study was to evaluate the feasibility of building machine learning models to predict the need for preclinical airway management in trauma patients. As a first step, attributes of the MIND that define patients who need preclinical airway management were identified. Second, two machine learning algorithms were tested to demonstrate the accuracy of the models.

METHODS

Ethical statements

This study is reported based on the TRIPOD (Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis) statement.[12] The trial was approved by the Ethics Committee of the State Medical Association of Rhineland-Palatinate (No. 2021-15767-retrospektiv). The study is a retrospective registry analysis with anonymized data. Informed consent was waived due to the retrospective nature of the study.

Design and setting

Adult patients with multiple injuries who were primarily treated by a physician-staffed ground or air ambulance from 2018 to 2020 were selected from the MIND. Dead patients and those requiring resuscitation were excluded. Briefly, the MIND files of the remaining patients were preprocessed for attribute selection using medical causality and a principal component analysis (PCA). With the help of the resulting attributes, Naive Bayes (NB) and random forest (RF) models were trained and tested to find their accuracy in predicting whether those injured patients were given preclinical airway management. Patient selection, dataset creation, and the analyses are illustrated in Fig. 1.

Definition

The MIND does not yet contain anesthesia as an attribute. Therefore, emergency general anesthesia in any injured patient was defined as documentation of invasive airway management, positive end tidal CO_2 without noninvasive ventilation (NIV) at admission, documented invasive ventilation at admission and the use of a muscle relaxant, or any use of a muscle relaxant. The main assumption was the correct indication of preclinical emergency anesthesia.

Attribute selection and data preprocessing

The MIND includes more than 550 anonymized attributes, including specialization of the physician, standardized clinical examination findings, medical diagnoses, injury patterns in relation to particular body parts (classified as none, mild, moderate, severe, or deadly by the attending physicians), blunt or penetrating trauma, and vital signs at first contact and hospital admission, including the GCS, heart rate, systolic blood pressure, respiratory rate, oxygen saturation, end tidal CO_2, temperature, blood glucose level, and pain level. Furthermore, electrocardiogram findings (at first contact and hospital admission), medication (without dosage or timing), treatment (NIV, invasive airway management, thoracic drainage, pelvic sling), infusion therapy (crystalloid/colloid infusion, blood products), age, preemergency status (PES; a preclinically adapted classification of the American Society of Anesthesiologists), time on site, and transport time are recorded in the dataset.[13]

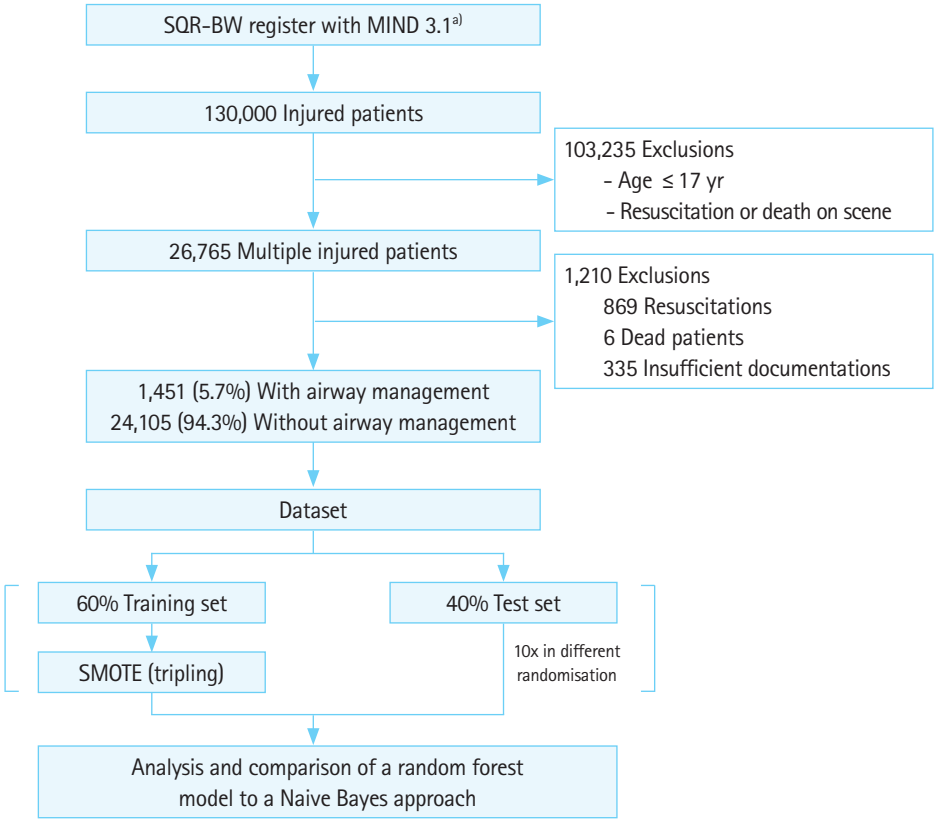

Fig. 1. Flowchart for patient selection, dataset creation, and analysis. SQR-BW, Center for Quality Management in Emergency Medical Services Baden-Wuerttemberg; MIND, minimal emergency dataset; SMOTE, synthetic minority oversampling method. a)A total of 24 attributes included: >550 attributes filtered by causality or potential correlation, then selected by principal component analysis (Wrapper).

The datasets of patients with cardiac arrest were excluded because abstaining from resuscitation could bias the weighting of certain attributes. Only datasets with at least two of the following three attributes, initial GCS, systolic blood pressure, and oxygen saturation, were included because those parameters represent the guidelines' recommendations.[1-3]

In data preprocessing, generally accepted attributes in the training set with potential correlations but no medical causality were excluded from the machine learning analysis (e.g., place of accident), as were causal attributes without any frequent occurrence in one of the two classes. Attributes correlating with indications for airway management were identified using international guidelines about respiratory, neurological, or hemodynamic findings and injury patterns.[2,3,14] However, because critical volume loss and (developing) shock are not directly recorded in the MIND, surrogate parameters such as pelvic sling or tranexamic acid were also included.

The imputation of missing data was not considered due to the nominal character of most attributes. Because the remaining attributes all contributed with different weightings, a PCA was performed on the whole dataset using the wrapper method with a bidirectional search and a C4 decision tree (J48) with tenfold cross-validation (settings in Supplementary Table 2).[15] The Java-based software Weka ver. 3.8.4 (University of Waikato, Hamilton, New Zealand) was used for the PCA and machine learning.[16,17] Statistical comparison of the attributes between the two classes (airway management and no airway management) was performed with chi-square test, U-test, or t-test, as appropriate, in Microsoft Excel (Microsoft Corp., Redmond, WA, USA). A P-value of less than 0.05 was defined as significant. Continuous variables are expressed as means and standard deviations, and categorical variables are expressed as percentages.

Class balancing, training, and testing

The data were split into a 60% training set and 40% test set 10 times with a randomized split procedure to define the performance of the algorithms with different frequencies of invasively ventilated patients. In general, machine learning algorithms tend to learn and predict the majority class, whereas most studies are interested in the minority class. To handle that class imbalance problem for the minority class that received airway management, the synthetic minority oversampling method (SMOTE) algorithm was used to triple the airway management class in the training sets, but not in the test sets. SMOTE synthesis creates one new minority instance out of k = 5 existing minority instances using the k-nearest neighbor approach (Supplementary Table 3).[18] This procedure was chosen because Weka does not offer a cross-validation that uses SMOTE in training but not in testing. Tripling the minority class was an appropriate assessment to improve the predictions and prevent overfitting. For supervised machine learning, the NB and RF methods were chosen (Supplementary Table 4). Both algorithms can handle missing values.

Model performance

All results are presented as means with 95% confidence intervals (CIs). As performance criteria, overall correctness, kappa value, the area under the receiver operator curve (AUC-ROC), sensitivity (need for airway management), specificity (no need for airway management), positive predictive value (PPV) and negative predictive value (NPV), and the precision-recall (PRC) area were chosen.[15] The Matthews correlation coefficient (MCC) was used to measure the quality of the two presented classes of very different sizes (range: −1, total disagreement; 0, random prediction; +1, perfect prediction).[19] The cost-benefit calculation for the RF algorithm was performed automatically for the lowest overall error rate. The performance across all 10 test sets was averaged and compared with a t-test ($P < 0.05$ as significant, calculated in Microsoft Excel).

RESULTS

Out of more than 130,000 injured patients, 26,765 patients with multiple injuries were selected. Of the selections, 869 resuscitations, 6 fatal cases, and 335 insufficiently documented datasets were then excluded, leaving 25,556 datasets with 1,451 cases (5.67%) of airway management.

Data preprocessing identified 31 attributes with potential correlation or medical causality. In the PCA, 24 attributes were selected, among them auscultation, injury pattern without the upper limbs or soft parts, oxygen therapy, NIV, tranexamic acid and catecholamines, pelvic sling, vital signs, PES, and shock index. With the exception of initial systolic blood pressure and respiratory rate ($P > 0.05$), the groups with and without airway management differed significantly (Table 1). For further information about nonselected attributes see Supplementary Table 1.

In overall correctness, the RF outperformed the NB (97.8 [95% CI, 97.57–98.03] vs. 93.55 [95% CI, 93.11–93.99], respectively; $P < 0.01$). The RF reached a significantly higher kappa value (0.78 [95% CI, 0.75–0.8]) than the NB (0.54 [95% CI, 0.52–0.56]; $P < 0.01$). In the AUC-ROC analysis, the RF reached 0.96 (95% CI, 0.96–0.97), and the NB reached 0.93 (95% CI, 0.92–0.93; $P < 0.01$) (Fig. 2A). Furthermore, the RF model had a significantly higher MCC than the NB approach (0.78 [95% CI, 0.76–0.8] vs. 0.56 [95% CI, 0.54–0.57], respectively; $P < 0.01$).

Table 1. Clinical findings and medical treatments for both classes with the attributes selected through the principal component analysis

Attribute	Airway management		P-value
	Yes (n = 1,451)	No (n = 24,105)	
Auscultation 1			< 0.01[a]
Obstruction/gasping/apnea	15.0	0.3	
Bronchial spasm	18.0	0.3	
Rhonchi	2.0	0.2	
Other	31.0	13.0	
Auscultation 2			
Dyspnea ± cyanosis	37.0	3.0	< 0.01[a]
Head injury			
None	36.0	65.0	< 0.01[a]
Mild	5.0	20.0	< 0.01[a]
Moderate	15.0	13.0	0.05[a]
Severe	44.0	2.0	< 0.01[a]
Face injury			< 0.01[a]
None	77.0	83.0	
Mild	5.0	10.0	
Moderate	11.0	7.0	
Severe	7.0	0.6	
Cervical spine injury			
None	90.0	88.0	0.07
Mild	2.0	6.0	< 0.01[a]
Moderate	4.0	5.0	0.40
Severe	4.0	0.7	< 0.01
Thoracic/lumbar spine injury			< 0.01[a]
None	90.0	85.0	
Mild	1.0	5.5	
Moderate	4.0	8.0	
Severe	4.0	1.0	
Thoracic injury			
None	68.0	77.0	< 0.01[a]
Mild	3.0	9.0	< 0.01[a]
Moderate	10.0	12.0	0.10
Severe	19.0	2.0	< 0.01[a]
Abdominal injury			
None	85.0	92.0	< 0.01[a]
Mild	1.0	2.0	< 0.01[a]
Moderate	4.0	4.0	0.50
Severe	10.0	1.0	< 0.01[a]
Pelvic injury			
None	83.0	87.0	< 0.01[a]
Mild	2.0	5.0	< 0.01[a]
Moderate	4.0	6.0	0.02[a]
Severe	1.0	2.0	< 0.01[a]
Lower limb injury			< 0.01
None	76.0	72.0	
Mild	4.0	12.0	
Moderate	7.0	12.0	
Severe	13.0	3.0	
Oxygen therapy	57.0	35.0	< 0.01[a]
Noninvasive ventilation	32.0	0.2	< 0.01[a]
Thoracic drainage	14.0	0.2	< 0.01[a]
Colloid infusion	7.0	0.2	< 0.01[a]
Tranexamic acid	40.0	4.0	< 0.01[a]
Pelvic sling	27.0	4.0	< 0.01[a]
Catecholamine	43.0	1.0	< 0.01[a]
Systolic blood pressure (mmHg)	137 ± 29	138 ± 28	0.29
Oxygen saturation (%)	94 ± 7	95 ± 6	< 0.01[a]
Heart rate (beats/min)	90 ± 20	89 ± 19	< 0.01[a]
Respiratory rate (breaths/min)	16 ± 5	16 ± 5	0.24
Pain level (0–10)[b]	5 (0–10)	5 (0–10)	< 0.01[a]
Shock index	0.7 ± 0.3	0.6 ± 0.6	0.03[a]
Preemergency status (1–4)[c]	2 (1–3)	2 (1–3)	< 0.01[a]
Glasgow Coma Scale (3–15)	15 (14–15)	15 (15–15)	< 0.01[a]
Age (yr)[d]	54.88 ± 21.44	55.80 ± 22.28	0.13
Male sex[d]	72.0	60.0	< 0.01[a]

Values are presented as percentage, mean ± standard deviation, or median (interquartile range).
[a]Statistically significant value (P < 0.05). [b]No pain, 0. [c]Healthy, 1; moribund, 4. [d]Baseline characteristics not used in the algorithm.

In predicting the use of airway management, the difference between the NB and RF results was not statistically significant (0.75 [95% CI, 0.73–0.76] vs. 0.73 [95% CI, 0.71–0.76], respectively; P = 0.38). The best PPV was gained with the RF (0.85 [95% CI, 0.84–0.87]; NB, 0.46 [95% CI, 0.44–0.49]; P < 0.01). This also resulted in a larger PRC area for the RF (0.83 [95% CI, 0.80–0.85]; NB, 0.66 [95% CI, 0.61–0.72]; P < 0.01) (Fig. 2B).

Both algorithms yielded a very high specificity (RF, 0.993 [95% CI, 0.992–0.994] vs. NB, 0.947 [95% CI, 0.942–0.952]; P < 0.01), a high NPV (RF, 0.984 [95% CI, 0.980–0.987] vs. NB, 0.984 [95% CI, 0.983–0.985]; P = 0.85), and a high PRC area (RF, 0.996 [95% CI, 0.996–0.997] vs. NB, 0.992 [95% CI, 0.992–0.993]; P < 0.01) (Table 2).

The average threshold of the RF model was 0.51 (95% CI, 0.49–0.53). Due to the decision process used by the NB, no average threshold can be given for it. The three most important attributes in the RF were systolic blood pressure (0.306 ± 0.019), head injury (0.305 ± 0.013), and initial heart rate (0.294 ± 0.018) (Fig. 3).

DISCUSSION

This study set out to develop a decision model for determining the necessity of preclinical airway management in adult trauma patients. Commonly recorded preclinical attributes such as injury pattern, certain examination findings, vital signs, and emergency medical interventions were found to be most influential in forecasting the need for preclinical airway management. Both models

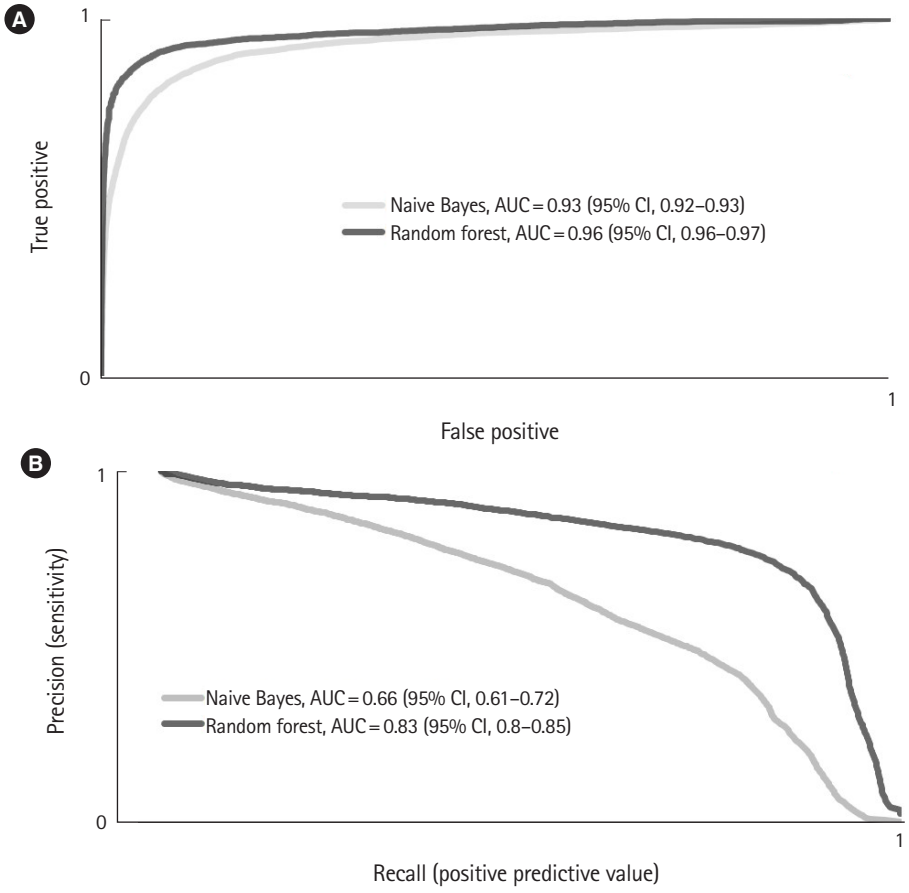

Fig. 2. Averaged (A) receiver operator curves for the overall performance and (B) precision-recall curves for the prediction of airway management by the Naive Bayes and random forest algorithms. AUC, area under the curve; CI, confidence interval.

Table 2. Model performance and evaluation of random forest versus Naive Bayes

Variable	Random forest	Naive Bayes	P-value
Overall correctness (%)	97.80 ± 0.37 (97.57–98.03)	93.55 ± 0.71 (93.11–93.99)	< 0.01[a]
Kappa	0.78 ± 0.04 (0.75–0.80)	0.54 ± 0.03 (0.52–0.56)	< 0.01[a]
AUC-ROC	0.96 ± 0.01 (0.96–0.97)	0.93 ± 0 (0.92–0.93)	< 0.01[a]
MCC	0.78 ± 0.04 (0.76–0.80)	0.56 ± 0.02 (0.54–0.57)	< 0.01[a]
Sensitivity	0.73 ± 0.05 (0.71–0.76)	0.75 ± 0.02 (0.73–0.76)	0.38
Positive predictive value	0.85 ± 0.03 (0.84–0.87)	0.46 ± 0.03 (0.44–0.49)	< 0.01[a]
PRC area[b]	0.83 ± 0.04 (0.80–0.85)	0.66 ± 0.09 (0.61–0.72)	< 0.01[a]
Specificity	0.993 ± 0.002 (0.992–0.994)	0.947 ± 0.008 (0.942–0.952)	< 0.01[a]
Negative predictive value	0.984 ± 0.006 (0.980–0.987)	0.984 ± 0.001 (0.983–0.985)	0.85
PRC area[b]	0.996 ± 0.001 (0.996–0.997)	0.992 ± 0.001 (0.992–0.993)	< 0.01[a]

Values are presented as standard deviation (95% confidence interval).
AUC-ROC, area under the receiver operator curve; MCC, Matthews correlation coefficient; PRC, precision-recall.
[a]Statistically significant value ($P < 0.05$). [b]Given for the prediction and exclusion of airway management.

developed here showed excellent results in excluding the need for airway management, but only the RF model had satisfactory accuracy in predicting it. Therefore, the feasibility of using machine learning to predict the need for airway management in preclinical trauma patients has been confirmed, but the models need to be advanced. Nonetheless, even before a final model can be implemented in the electronic medical records, the attributes determined here can already be used clinically to alert emergency physicians about trauma patients at increased risk of requiring airway management. For example, the absence of severe head or

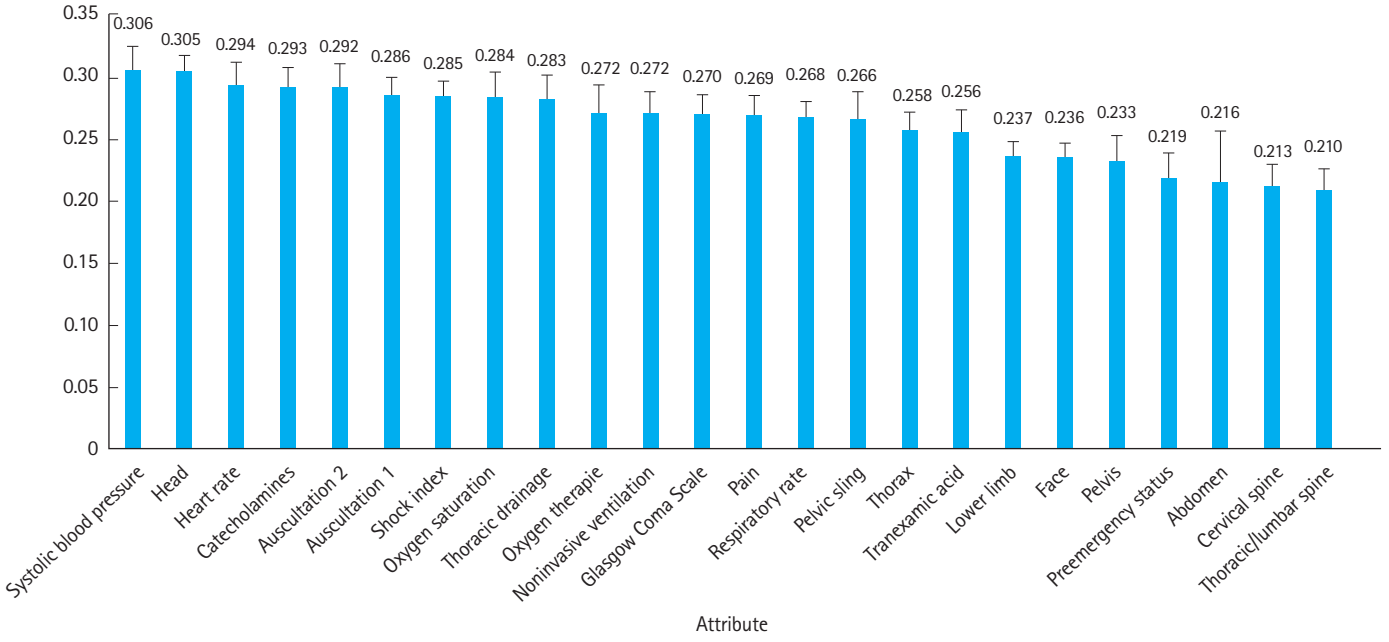

Fig. 3. Attribute weighting in the random forest model, given as means with standard deviation error bars.

thoracic injury, catecholamine therapy, thoracic drainage, or NIV could justify a later evaluation of airway protection. To the best of our knowledge, this analysis is the first to use machine learning to forecast airway management in a preclinical environment. However, several factors need to be considered to interpret and advance the results.

Database, attribute selection, and model comparison

The more distinct the pathological findings in the initial parameters, the better the classification by the algorithms could be. However, differences in attributes such as GCS or oxygen saturation were marginal, and their averages were physiological, which was partly reported in other clinical modeling studies.[8,20,21] This could be explained by belated documentation of paramedically stabilized vital signs.

Attribute choice is always a compromise between overgeneralization (selecting only attributes with strong correlation or causality) and overfitting (selecting many attributes, even those with weak correlation). The PCA in this study filtered in attributes with strong indirect correlations with airway management. For example, the use of catecholamines can be interpreted as a surrogate for hemodynamic instability before or after airway management in emergency anesthesia. Other surrogates were colloid infusion, pelvic sling, and tranexamic acid for potential blood loss (attribute tourniquet not included in MIND). NIV can be discussed as a surrogate for respiratory failure or a method of preoxygenation. Although the shock index is only to some extent reliable for the diagnosis of shock, it had weight in combination with other attributes.[22,23] Because preclinical emergency physicians in Germany usually lack point-of-care and radiographic findings, they have to use a less-reliable clinical examination with baseline vital signs for their time-critical decision-making. The surrogate parameters used in this study can therefore be seen as a replacement for real-time vital signs. They also reflect to some extent the recommendations for airway management in patients with traumatic respiratory disorder, brain injury, and shock.[1-3] Future prediction models in preclinical airway management should combine attributes emphasized in the guidelines with selected surrogates that reflect the dynamics of preclinical emergency medicine to compensate for any lack of real-time parameters.

Compared with other studies, a main distinction of this study is the restriction to initial vital signs and adaptation to preclinical conditions.[2,3] Siu et al.[20] used an additional blood gas analysis with sequential organ failure assessments at multiple time points for their RF model to predict the need for intubation in the first 24 hours after a critical care admission (sensitivity, 0.88; specificity, 0.66; AUC-ROC, 0.86; PPV, 0.73; NPV, 0.85). Arvind et al.[6] indicated a AUC-ROC of 0.84 and PRC area of 0.3 for their RF model for predicting mechanical ventilation in COVID-19 patients based on vital signs and a blood gas analysis. In neonatal intensive care, Clark et al.[8] demonstrated a boosted logistic regression model with an AUC-ROC of 0.84. Politano et al.[21] could predict urgent intubation in a trauma intensive care unit with an AUC-ROC of 0.770 to 0.865 with the help of a boosted logistic regression us-

ing multiple sampling windows for vital signs along with age, oxygen partial pressure, and days since extubation.

Model performance

With regard to the performance of both algorithms, several factors about their basic method of calculation and the prevalence of airway management must be considered. In this study, the ROC curve alone overestimates the model performance because of the class imbalance problem (94% without emergency anesthesia) and the very high specificities and negative predictive values. Therefore, the goodness of class prediction can best be evaluated by the PRC area, which showed that the RF had a robust predication accuracy.[24]

The basic assumption of the NB is the independence of all attributes without any correlation. Such a level of independence is almost never found in real-world data. In this study, the auscultation findings, respiratory rate, and oxygen saturation all influence one another, as do the GCS score and face and/or head injury. The decision process in favor of or against a class is performed by comparing the summed probability of the test case to the summed probability of the class, which leads to the shown bad calibration. The advantage of an NB approach is its fast calculation and simple implementation. Also, the arithmetic means and variance are parameterized independently of all other variables.[15]

Unlike in the NB, independence is not a basic assumption of an RF. Decision trees have the advantage of using the same attributes on different levels in different dependencies. In contrast to a single decision tree model, an RF uses the bagging procedure, by which multiple random trees each calculate a prediction. Those are then averaged to reach a final decision. This explains not only why RF got better outcomes than NB but also the weights of certain attributes whose differences were marginal. Those same effects also appear in the PCA, because it also uses a decision tree model. Therefore, the RF is robust to outliers, works well with nonlinear data, and has a lower risk of overfitting than single decision trees. As a result, the RF could handle even the relatively small prevalence of airway management cases in the test sets, achieved a good PRC area, and had a robust performance.[15,25] Given the prevalence between the different test sets, the RFs differ, and a final model cannot be given.

Further limitations

Due to the former and following limitations, this study represents only a first attempt to build a sustainable, general model for predicting preclinical airway management. Overreliance on machine learning in high-risk situations can result in potential patient hazards. Future models are also needed for internal and neurological patients. These results were developed in a physician-staffed emergency medical system and therefore cannot be simply transferred to paramedic systems.[26] The weighting of certain attributes could be changed by alterations in clinical practice. The timing of interventions is missing from MIND, which limits the applicability of the models presented here. Unlike previous prediction models for resuscitation, attributes such as trauma site were not included in the data used here. Whereas in resuscitation, the site of cardiac arrest is directly linked to bystander cardio-pulmonary resuscitation, there is no such correlation for trauma site or mechanism and airway management, only for trauma severity.[3,27] Unfortunately, that severity can only be assessed by the primary physical exam and not by later radiographic findings and hospital data. Although this study used data from a statewide emergency medical service, no independent external test set from another German region was used here. Therefore, predications of stability with regard to noise and overfitting must be restrained. Unlike in other studies, the imputation of missing values in this study was not reasonable, mainly due to static nominal, binary, or ordinal attributes.[6,20] Whether emergency physicians postponed endotracheal intubation because of a potentially difficult airway or a lack of experience cannot be stated because no further clinical records were available.[5] Also, the correct indication for airway management and primary assessment according to the ABCDE algorithm could not be checked in every single case due to the retrospective design and dataset structure. In machine learning, unsupervised deep learning neural networks have recently outperformed supervised approaches such as the RF. However, those deep learning models require a large amount of data and computing power. Network creation is complex, unstandardized, and time-consuming. Because this study focused on a simple binary problem, and the data structure was inconsistent, RF and NB were chosen. The supplementary data contain a first approach to a deep learning neural network, but it performed worse than the RF in predicting the need for airway management (Supplementary Table 5 and Supplementary Fig. 1). Nonetheless, a deep learning application might be suitable for future models, especially with real-time attributes.[15]

CONCLUSION

In conclusion, this study has shown the feasibility of using a machine learning model to predict the need for airway management in injured patients. The RF model combined a satisfactory prediction performance with an excellent ability to exclude the need for airway management in trauma patients. Because the many attributes available can be a hindrance in quickly assessing trauma patients, models such as those presented here could already

be used as surveillance tools in the background or to send the intubation probability to the hospital, where additional resources could be activated. Embedded in a continuous electronic medical record and expanded by data about internal patients, real-time parameters and point-of-care tests, an RF-based prediction model could be made more reliable and support preclinical decision-making or quality management. In the future, patients at risk could be identified at an early time with the help of such a machine learning model.

SUPPLEMENTARY MATERIAL

Supplementary Table 1. All recorded attributes and their values together with the class comparison and reason for exclusion
Supplementary Table 2. Settings of the principal component analysis in Weka
Supplementary Table 3. Settings of the SMOTE algorithm in Weka
Supplementary Table 4. Settings of the random forest and Naive Bayes model in Weka
Supplementary Table 5. Performance of two deep learning networks before and after attribute selection
Supplementary Fig. 1. Averaged receiver operator curves (ROC) for (A) the overall performance and (B) the averaged precision-recall (PRC) curves for the prediction of airway management of the Naive Bayes, the random forest algorithm, and the deep learning neural network (one dense layer with six neurons) after attribute selection.
Supplementary materials are available at https://doi.org/10.15441/ceem.22.335. Further supplementary data, including single random forest models, are available upon reasonable request via e-mail. Due to data protection, the datasets cannot be published, but research with the database is possible upon request to the Center for Quality Management in Emergency Medical Services Baden-Wuerttemberg (SQR-BW).

CONFLICT OF INTEREST

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

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AUTHOR CONTRIBUTIONS

Conceptualization: AL; Data curation: AL, TL, JE; Formal analysis: AL; Funding acquisition: WZ; Investigation: AL; Methodology: AL; Project administration: TV; Resources: TL, JE; Software: AL; Supervision: WZ, MT, TV; Validation: AL; Visualization: AL; Writing–original draft: AL; Writing–review & editing: WZ, TL, JE, MT, TV.
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Supplementary Table 1. All recorded attributes and their values together with the class comparison and reason of exclusion

Attribute	Airway management		P-value	Reason of exclusion
	Yes (n = 1,451)	No (n = 24,105)		
Trauma site				No causality
Unknown	1.31	0.71	0.01[a]	
Home	24.60	28.43	< 0.01[a]	
Retirement home	2.00	3.07	0.02[a]	
Workplace	7.79	6.84	0.16	
Medical practice	0.21	0.54	0.09	
Street	44.59	44.31	0.80	
Public space	10.61	8.97	0.03[a]	
Hospital	1.45	1.24	0.48	
Mass event	0.14	0.19	0.67	
Educational institution	2.83	0.87	< 0.01[a]	
Sport facility	1.03	1.47	0.18	
Birth center	0.55	0.39	0.33	
Other	2.89	2.98	0.80	
Transportation				No causality
Ground	59.06	86.34	< 0.01[a]	
Air	1.59	1.82	0.50	
Ambulant	39.35	11.84	< 0.01[a]	
Emergency vehicle			< 0.01[a]	No causality
Ground ambulance	55.75	89.36		
Air ambulance	44.25	10.64		
Specialist and qualification				Preprocessing, left out for generalization
Anesthetist	65.61	53.58	< 0.01[a]	
Anesthetist with qualification in intensive care medicine	12.68	10.14	< 0.01[a]	
Other	19.92	33.34	< 0.01[a]	
Other with qualification in intensive care medicine	1.79	2.94	0.01[a]	
State of awareness				Preprocessing
Other	0.34	0.40	0.75	
Awake	69.06	84.22	< 0.01[a]	
Unconscious	5.93	1.50	< 0.01[a]	
Reacts to speech	7.51	6.16	0.04[a]	
Reacts to pain	3.86	1.90	< 0.01[a]	
Sedated	7.31	1.56	< 0.01[a]	
Unknown	6.00	4.26	< 0.01[a]	
Dementia				No causality
Yes	0.76	1.39	< 0.01[a]	
No	99.24	98.61		
Pathologic neurologic examination			< 0.01[a]	Preprocessing
Yes	9.92	6.47		
No	90.08	93.53		
Skin				Preprocessing
Other	11.99	8.60	< 0.01[a]	
Normal	29.57	66.85	< 0.01[a]	
Exsiccosis	1.31	3.56	< 0.01[a]	
Oedema	0.41	0.61	0.35	
Cold sweat	9.51	4.11	< 0.01[a]	
Missing value	47.21	16.28	< 0.01[a]	
Aggressive			0.30	Preprocessing
Yes	8.34	7.57		
No	91.66	92.43		

(*Continued on the next page*)

Supplementary Table 1. (Continued)

Attribute	Airway management		P-value	Reason of exclusion
	Yes (n = 1,451)	No (n = 24,105)		
Confusion			< 0.01[a]	Preprocessing
Yes	9.10	12.75		
No	90.90	87.25		
Acute CNS deficiency				Preprocessing
None	96.76	97.64	0.03[a]	
Seizure	1.03	1.03	0.99	
Stroke/bleeding	2.14	0.93	< 0.01[a]	
Other	0.07	0.39	0.049[a]	
Pulmonary embolism			0.50	Too rare
Yes	0	0.03		
No	100	99.97		
Acute cardiac disease			< 0.01[a]	Too rare
Yes	1.38	2.61		
No	98.62	97.39		
Bronchial spasm			0.10	Too rare
Yes	0	0.16		
No	100	99.84		
Aspiration/hemoptysis				
Yes	0.76	0.02	< 0.01[a]	Too rare
No	99.24	99.98		
Pneumothorax			0.04[a]	Too rare
Yes	0.07	0.01		
No	99.93	99.99		
Intoxication			< 0.01[a]	Too rare
Yes	0.90	2.15		
No	99.10	97.85		
Anaphylaxis			0.34	Too rare
Yes	0	0.06		
No	100	99.94		
Sepsis			0.48	Too rare
Yes	0	0.03		
No	100	99.97		
Hypothermia/hyperthermia			0.39	Too rare
Yes	0.69	0.52		
No	99.31	99.48		
Palliative condition			0.50	Too rare
Yes	0	0.02		
No	100	99.98		
Acute infection			0.40	Too rare
Yes	0.14	0.23		
No	99.86	99.77		
Acute abdomen			0.20	Too rare
Yes	0.41	0.26		
No	99.59	99.74		
Acute nontraumatic disease (summarized)			0.02[a]	Too rare
Yes	9.17	11.06		
No	90.83	88.94		
Upper limb			< 0.01[a]	Wrapper
None	80.36	64.33		
Mild	4.96	16.64		
Moderate	8.68	16.66		
Severe	6.00	2.37		

(*Continued on the next page*)

Supplementary Table 1. (Continued)

Attribute	Airway management		P-value	Reason of exclusion
	Yes (n = 1,451)	No (n = 24,105)		
Severe limb trauma (summarized)			< 0.01[a]	Wrapper
Yes	15.58	3.99		
No	84.42	96.01		
Soft parts				Wrapper
None	89.32	93.03	< 0.01[a]	
Mild	3.58	4.52	0.10[a]	
Moderate	3.79	1.98	< 0.01[a]	
Severe	3.31	0.47	< 0.01[a]	
Burn			< 0.01	Too rare
Yes	1.17	0.48		
No	98.83	99.52		
Acute inhalation injury			< 0.01	Too rare
Yes	0.76	0.11		
No	99.24	99.89		
Electrical accident			0.80	Too rare
Yes	0.14	0.12		
No	99.86	99.88		
Chemical burn			0.60	Too rare
Yes	0	0.02		
No	100	99.98		
Diving accident			0.35	Too rare
Yes	0	0.01		
No	100	99.99		
Other trauma			0.35	Too rare
Yes	1.10	1.40		
No	98.90	98.60		
Neck collar			< 0.01[a]	Wrapper
Yes	63.89	33.36		
No	36.11	66.64		
Mechanism of trauma				No causality
Blunt	57.89	78.45	< 0.01[a]	
Penetrating	4.14	5.58	0.02[a]	
Unknown	37.97	15.96	< 0.01[a]	
Circumstances of trauma				No causality, further details needed
Biker	11.65	9.94	0.03[a]	
Violent felony	4.48	1.68	< 0.01[a]	
Vehicle occupant	18.47	17.47	0.30	
Pedestrian	3.79	4.28	0.37	
Fall				
< 3 m	24.47	30.98	< 0.01[a]	
> 3 m	10.54	7.60	< 0.01[a]	
Bicyclist	12.06	11.82	0.78	
Assault	1.72	1.40	0.31	
Stabbed	0.34	0.64	0.16	
Shot	0	0.06	0.34	
Machine accident	0.55	0.71	0.47	
Burying	0.34	0.18	0.15	
Other modes of transport	0.83	0.92	0.71	
Other	4.89	6.37	0.02[a]	
Unknown	5.86	5.93	0.43	

(*Continued on the next page*)

Supplementary Table 1. (Continued)

Attribute	Airway management		P-value	Reason of exclusion
	Yes (n = 1,451)	No (n = 24,105)		
Crystalloid infusion			< 0.01[a]	Too general
Yes	93.87	86.02		
No	6.13	13.98		
Blood products			< 0.01[a]	Too rare
Yes	0.55	0.01		
No	99.45	99.99		
Blood glucose level (mg/dL)	159.77 ± 101.29	139.51 ± 81.73	< 0.01[a]	No causality
Age (yr)	54.88 ± 21.44	55.8 ± 22.28	0.13	Wrapper
Temperature (°C)	37.59 ± 9.28	38.38 ± 36.5	0.14	No causality
Systolic blood pressure < 90 mmHg			< 0.01[a]	Preprocessing
No	93.59	96.22		
Yes	6.41	3.78		
Glasgow Coma Scale < 9			< 0.01[a]	Preprocessing
No	85.87	96.67		
Yes	14.13	3.33		
Transport time (min)	10.58 ± 10.13	11.28 ± 10.53	0.01	No causality
Total	35.15	26.61	< 0.01[a]	Preprocessing
< 10	32.67	33.60		
11–20	7.31	12.45		
21–30	3.65	3.37		
31–45	1.03	0.85		
> 45	20.19	23.11		
Time on side (min)	24.32 ± 19.75	20.35 ± 14.97	< 0.01[a]	No causality
Total	6.00	12.56	< 0.01[a]	Preprocessing
< 15	41.42	45.48		
15–30	22.81	17.23		
31–45	8.34	3.51		
46–60	2.69	1.07		
> 60	18.75	20.15		
Prehospital time (min)	44.81 ± 38.25	41.40 ± 36.75	< 0.01[a]	No causality
Total	1.03	2.24	< 0.01[a]	Preprocessing
< 30	9.65	13.76		
30–45	23.64	24.07		
46–60	29.22	24.31		
61–90	6.27	4.73		
> 90	30.19	30.89		
Male sex	72.00	60.00	< 0.01[a]	No causality

Values are presented in percentage or mean ± standard deviation.
Some attributes were combined because they appeared too rarely. For example, the diagnosis of hypertensive emergency, pulmonary oedema, myocardial infarction, and other acute cardiac diseases were combined to "acute cardiac disease."
CNS, central nervous system.
[a]Statistically significant value (P < 0.05).

Supplementary Table 2. Settings of the principal component analysis in Weka

Setting	Principal component analysis	J48
Classifier	J48	-
Do not check capabilities	False	False
Evaluation measure	Accuracy	-
Calc out of bag	False	-
No. of folds	5	3
Threshold	0.01	-
Search method	Best first	-
Best first direction	Bidirectional	-
Lookup cache size	1	-
Search termination	5	-
Batch size	-	100
Binary splits	-	False
Collapse tree	-	True
Confidence factor	-	0.25
Debug	-	False
No. of decimal places	-	2
Do not make split point actual value	-	False
Reduced error pruning	-	False
Save instance data	-	False
Subtree raising	-	True
Unpruned	-	False
Laplace smoothing	-	False
MDL correction	-	True

MDL, minimum description length.

Supplementary Table 3. Settings of the SMOTE algorithm in Weka

Setting	SMOTE
Class value	0 (Minority class)
Debug	False
Do not check capabilities	False
Nearest neighbors	5
Percentage	200

SMOTE, synthetic minority oversampling method.

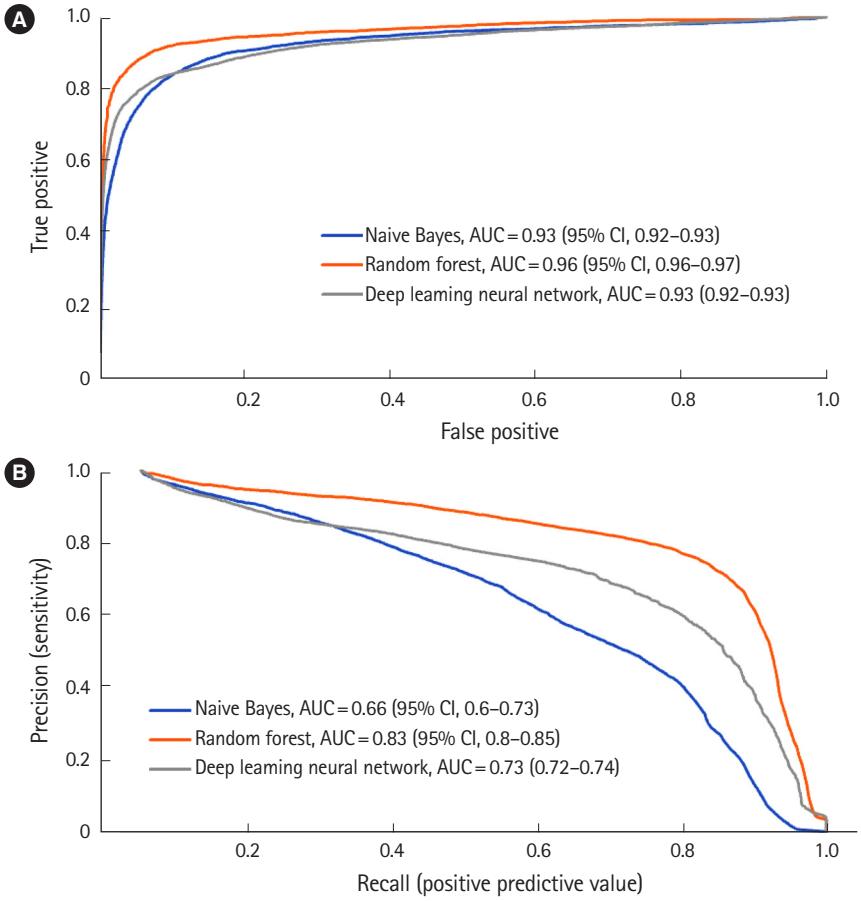
Supplementary Table 4. Settings of the random forest and Naive Bayes model in Weka

Setting	Random forest	Naive Bayes
Batch size	100	100
Break ties randomly	False	-
Calc out of bag	False	-
Debug	False	False
Do not check capabilities	False	False
No. of decimal places	2	2
Max depth	Unlimited	-
No. of execution slots	1	-
No. of randomly chosen attributes	0 (=log_2(#predictors)+1)	-
No. of iterations	100	-
Bag size percent	100	-
Supervised discretization	-	False
Kernel estimator	-	False

Supplementary Table 5. Performance of two deep learning networks before and after attribute selection

Variable	Deep learning neural network	
	Before attribute selection[a]	After attribute selection[b]
Overall correctness	96.51 ± 0.31 (96.29–96.73)	96.68 ± 0.17 (96.56–96.8)
Kappa	0.66 ± 0.03 (0.64–0.68)	0.68 ± 0.01 (0.67–0.69)
AUC-ROC	0.90 ± 0.01 (0.89–0.91)	0.93 ± 0.01 (0.92–0.93)
MCC	0.66 ± 0.03 (0.64–0.68)	0.68 ± 0.01 (0.67–0.69)
Sensitivity	0.73 ± 0.04 (0.70–0.75)	0.74 ± 0.04 (0.71–0.76)
Positive predictive value	0.64 ± 0.03 (0.61–0.66)	0.69 ± 0.09 (0.62–0.76)
PRC area	0.67 ± 0.03 (0.65–0.69)	0.73 ± 0.01 (0.72–0.74)
Specificity	0.95 ± 0.08 (0.89–1.01)	0.98 ± 0 (0.98–0.98)
Negative predictive value	0.99 ± 0 (0.98–0.99)	0.99 ± 0 (0.98–0.99)
PRC area	0.99 ± 0 (0.99–0.99)	0.98 ± 0.02 (0.97–1.00)

AUC-ROC, area under the receiver operator curve; MCC, Matthews correlation coefficient; PRC, precision-recall.
[a]Two dense layers with 30 neurons each. [b]One dense layer with six neurons.



Supplementary Fig. 1. Averaged receiver operator curves (ROC) for (A) the overall performance and (B) the averaged precision-recall (PRC) curves for the prediction of airway management of the Naive Bayes, the random forest algorithm, and the deep learning neural network (one dense layer with six neurons) after attribute selection. AUC, area under the curve; CI, confidence interval.

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Original Article

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The number and level of first-contact emergency medical services crew and clinical outcomes in out-of-hospital cardiac arrest with dual dispatch response

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Objective This study aimed to evaluate the association between the number and level of emergency medical technicians (EMTs) in the first-contact emergency medical services (EMS) unit and the clinical outcomes of out-of-hospital cardiac arrest (OHCA) with a dual dispatch response.

Methods Adult nontraumatic EMS-treated OHCAs between 2015 and 2018 in a nationwide database, were enrolled. The main exposure was the number and certification level of first-contact EMS crew: three versus two members, proportion of EMT intermediate level (EMT-I) over 50% versus under or equal to 50%. Good neurologic recovery was selected as the primary outcome. Multilevel multivariable logistic regression analysis was conducted to calculate adjusted odds ratios and confidence intervals.

Results A total of 26,867 patients were enrolled and analyzed. Good neurologic recovery was different across the study groups: 5.4% in the two-member crews, 7.2% in the three-member crews, 5.9% in the low EMT-I proportion crews, and 6.8% in the high EMT-I proportion crews. In the main analysis, statistically significant differences for favorable outcomes were found between the three-member and two-member crews, and the high EMT-I proportion and low EMT-I proportion crews; for good neurologic recovery, adjusted odds ratios (95% confidence interval) were 1.23 (1.06–1.43) for three-member crews, and 1.28 (1.17–1.40) for a high EMT-I proportion.

Conclusion The higher number and level of first-contact EMS crew was associated with better neurologic recovery in adult nontraumatic OHCA with a dual-dispatched EMS response.

Keywords Out-of-hospital cardiac arrest; Emergency medical services; Cardiopulmonary resuscitation

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Capsule Summary

What is already known

The number of emergency medical services (EMS) providers and proportion of high-level EMS providers at the scene is associated with clinical outcomes in out-of-hospital cardiac arrest (OHCA).

What is new in the current study

In dual dispatch response-treated OHCA, number and level of EMS providers in the first-contact EMS unit affects clinical outcomes.

INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) is a major public health concern.[1,2] OHCA incidence increases every year, and the worldwide survival rate remains at approximately 10%.[3-5] Many studies have been conducted to improve OHCA outcomes, and rapid defibrillation, a short ambulance response time, and high-quality cardiopulmonary resuscitation (CPR) have been found to be core elements in prehospital resuscitation.[6-9]

A dual dispatch response (DDR) system of emergency medical services (EMS), which dispatches multiple vehicles to the scene, has been applied in many countries to improve outcomes.[10,11] Dispatching multiple vehicles to a scene is associated with shorter EMS response time, which is the elapsed time interval between EMS activation and ambulance scene arrival, and a better prognosis.[11-13] Additionally, early defibrillation and a higher defibrillation rate are the other positive effects of multiple vehicle dispatch on clinical outcomes.[14-16] DDR has been shown to increase the number of on-scene EMS personnel, leading to better quality CPR and application of advanced procedures that improve survival outcomes.[17,18]

The number and certification level of on-scene emergency medical technicians (EMTs) have been evaluated for their impact on OHCA outcomes. Higher number of EMTs and a higher ratio of high-level EMTs at the scene have been associated with better survival outcomes.[18-20] Tsai et al.[21] reported that a larger number of EMTs is needed to provide optimal teamwork performance and advanced procedures. However, other studies found no significant association between the number of EMS crew members and clinical outcomes,[22-25] thus, this effect remains controversial.

In a DDR setting, EMS units are divided into first-contact and second-contact teams according to arrival time. A short response time and earlier advanced life support by the second EMS unit have been found to be associated with better outcomes.[26,27] However, the effect of the number and certification level of EMTs in the first-contact EMS unit have not been well evaluated. The purpose of this study was to evaluate the association between the number and level of EMTs in first-contact EMS units and the clinical outcomes of DDR-activated OHCA. We hypothesized that a higher number of EMS personnel and higher certification level proportion are associated with favorable outcomes.

METHODS

Ethical statements

This study complied with the Declaration of Helsinki, and its protocol was approved by the Institutional Review Board of Seoul National University Hospital with a waiver of informed consent (No. 1103-153-357).

Study design and data sources

This study is a retrospective observational cohort study based on a nationwide, prospective OHCA database in Korea from January 2015 to December 2018. This database system was developed in 2006 with the cooperation of the National Fire Agency and the Korea Centers for Disease Control and Prevention. In the database, EMS run-sheets and cardiac arrest registries that were recorded by the EMS crew immediately after OHCA transport and hospital record reviews collected by trained medical record reviewers were integrated. For DDR-activated cases, an additional multitier activation registry was filled out by the EMS crew or firefighters who did not transport victims.

Study setting

Korea, which has approximately 50 million residents within a land area of 100,210 km^2, has a government-operated EMS system. Under the National Fire Agency, a total of 17 provincial fire headquarters administer approximately 200 fire stations and 8,400 EMS personnel. For emergency calls, ambulances that are assigned to the EMS agencies belonging to the fire stations are dispatched

from the headquarters' dispatch centers.[28] The primary call dispatcher asks questions about altered mental status and abnormal breathing to identify cardiac arrest. For suspected OHCA, the call is passed to a medical call dispatcher to give CPR instructions.[29] The EMS CPR protocol at the scene and in the ambulance follows the American Heart Association guidelines.[30] Korean EMS workers provide basic-to-intermediate levels of intervention, including intravenous fluid administration and advanced airway management under physician-direct medical oversight. Because EMS crew members cannot pronounce a declaration of death, all EMS-treated OHCAs must be transported to the nearest emergency department (ED). EDs are designated as levels 1, 2, and 3 by the Ministry of Health and Welfare based on the case volume and quality of resources. Level 1 and 2 EDs must be staffed by emergency physicians 24/7 and have more resources.

DDR system

Since 2015, a DDR system has been implemented nationwide for suspected OHCA cases in Korea. The dispatcher asks two key questions for identification, consciousness, and respiration, and considers OHCA if both responses are abnormal. When the dispatcher suspects OHCA and activates DDR, a nearby ambulance and an additional available ambulance or fire engine could be dispatched. Ambulance selection is based on distance proximity only for both first-contact and second-contact EMS units, regardless of the number of EMS crews or certification level available. Each fire engine has two first responders, equivalent to emergency medical responder in United States, and provides a basic life support level of resuscitation with automated external defibrillators only. There are two certification levels of EMTs in the ambulance: EMT basic level (EMT-B) and EMT intermediate level (EMT-I). EMT-I can perform advanced airway and intravenous management under direct medical oversight. EMS providers with a nurse's license perform the same scope of work as EMT-I. The first arriving EMS crew starts chest compressions immediately and provides defibrillation when necessary. Advanced cardiovascular life support (ACLS) is provided when resources are sufficient because there is no definite protocol for ACLS timing. The first-contact EMS crew decides whether to activate DDR in cases where the victim's OHCA status was not recognized by the dispatcher.

Study population

EMS-treated adult OHCA cases from January 2015 to December 2018 were enrolled. We excluded cases where the cardiac arrest was witnessed in the ambulance, without EMS time information, where only fire engines or a single ambulance was dispatched, and where two ambulances arrived simultaneously.

Outcome measures

The primary outcome was good neurologic recovery, defined as cerebral performance category score 1 (no neurologic disability) or 2 (moderate disability, able to perform daily activities independently). Medical record reviewers determined patient scores based on discharge summary abstracts or physicians' medical record notes. Survival to discharge and prehospital return of spontaneous circulation were used as the secondary outcomes, respectively.

Variables and measurements

The main exposure of this study was the number and level of first-contact EMS crew. The first-contact EMS team was identified based on scene arrival time variables in the OHCA database. There were two or three members in each ambulance, including the driver participating in resuscitation at the scene, and the EMS crew members were either EMT-B or EMT-I (Fig. 1).

Demographic findings and clinical information were collected and categorized: age (≥ 65 years), sex, residential area (metropolitan area), location of cardiac arrest (public or private property), witnessed by bystander, bystander CPR, initial electrocardiogram rhythm (shockable), prehospital defibrillation, scene EMS management (advanced airway, intravenous access, and medication), EMS time interval (response time, scene time, and transport time), time interval between EMS unit arrivals (first-contact EMS unit and second-contact EMS unit), and level of ED (level 1, 2, or other).

Statistical analyses

Descriptive analysis was conducted to compare the distribution of demographic findings and clinical information according to the number and level of first-contact EMS crew. The level of first-

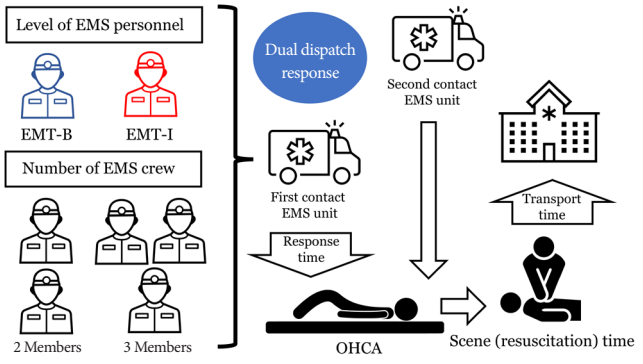

Fig. 1. Categorization of study groups according to the number and certification level of emergency medical services (EMS) crews in each ambulance in a dual dispatch. EMT-B, emergency medical technician basic level; EMT-I, emergency medical technician intermediate level; OHCA, out-of-hospital cardiac arrest.

contact EMS crew were categorized according to whether the EMT-I ratio within the ambulance was greater than 50%. The Wilcoxon rank-sum test was used to compare continuous variables, and the chi-squared test was used for the categorical variables. Univariable and multivariable logistic regression analyses by number and level of first-contact EMS crew were conducted to calculate adjusted odds ratios (AORs) and confidence intervals (CIs). Considering the nested nature of EMS operations according to districts, a multilevel analysis with a series of random-intercept models by 17 provincial headquarters was applied. Potential confounders, including age group, sex, residential area, location of cardiac arrest, witness status, bystander CPR, initial electrocardiogram rhythm, prehospital defibrillation, response time interval, time interval between EMS unit arrivals, transport time interval, number and level of second-contact EMS crew, and level of ED were adjusted for in the model.

We assumed the effect of the number of first-contact EMS crews can differ depending on the level of EMS providers in the unit. Interaction analysis by EMT-I proportion across the number of first-contact EMS crews was performed. A P-value <0.05 was considered significant for all analyses. All statistical analyses were performed using SAS ver. 9.4 (SAS Institute Inc., Cary, NC, USA) and R ver. 3.5 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Demographic findings

Among 112,999 EMS-treated OHCAs from 2015 to 2018, 26,867 victims were included in the final analyses. We excluded pediatric patients (n = 2,391), traumatic OHCA (n = 29,080), cardiac arrest witnessed in the ambulance (n = 5,696), missing time variables (n = 606), single dispatch response (n = 36,614), fire engine dispatched (n = 4,143), and no time difference between vehicles (n = 7,602) (Fig. 2).

Table 1 describes the demographic findings and clinical information according to the number and level of first-contact EMS crew members. In DDR cases, patients treated by a lower number of EMS personnel or low EMT-I proportion crew in the first-contact EMS unit were more likely to live in nonmetropolitan areas, undergo bystander CPR, and were less likely to receive an advanced procedure by EMS providers. Good neurologic recovery showed significant differences according to the number and level of first-contact EMS crew: 5.4% in the two-member EMS crews, 7.2% in the three-member EMS providers, 5.9% in the proportion of EMT-I under or equal to 50%, and 6.8% in the proportion of EMT-I over 50% (Table 1).

Main analyses

In the multivariable logistic regression model, statistically significant differences for the following favorable outcomes were found between three-member and two-member first-contact EMS units: AORs (95% confidence interval [CI]), 1.23 (1.06–1.43) for good neurologic recovery; 1.18 (1.07–1.31) for survival to discharge; and 1.29 (1.21–1.39) for prehospital return of spontaneous circulation (ROSC). EMT-I proportion over 50% showed a higher probability of favorable prognosis: AORs (95% CI), 1.28 (1.17–1.40) for good neurologic recovery; 1.16 (1.08–1.25) for survival to discharge; and 1.28 (1.17–1.40) for prehospital ROSC (Table 2).

In the interaction analysis, EMT-I proportion equal or under 50% showed a positive interaction effect with three EMS providers for good neurologic recovery compared with two EMS providers in the first-contact EMS units: AORs (95% CI), 1.26 (1.02–1.54) for good neurologic recovery in EMT-I equal or under 50%, and 1.07 (0.97–1.18) in EMT-I over 50% (Table 3 and Fig. 3).

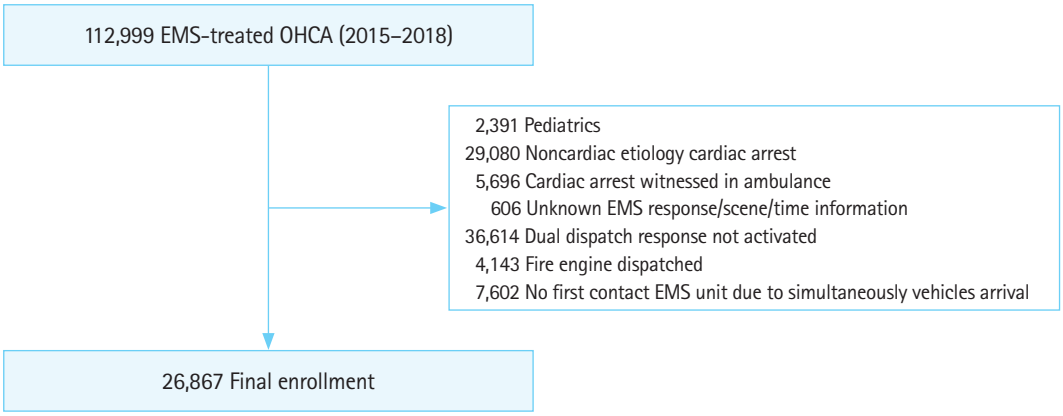

Fig. 2. Patient flow. EMS, emergency medical services; OHCA, out-of-hospital cardiac arrest.

Table 1. Study population demographics according to number and level of first-contact EMS unit

Characteristic	Total	No. of first-contact EMS crews			Proportion of EMT-I in first-contact EMS unit		
		Two EMS providers	Three EMS providers	P-value	≤ 50%	> 50%	P-value
Total	26,867 (100)	12,839 (47.8)	14,028 (52.2)	-	13,541 (50.4)	13,326 (49.6)	-
Age (yr)	59 (72–81)	59 (73–81)	58 (72–81)	0.087	58 (72–81)	59 (72–81)	0.328
≥ 65	16,905 (62.9)	8,115 (63.2)	8,790 (62.7)	0.355	8,544 (63.1)	8,361 (62.7)	0.547
Male sex	17,239 (64.2)	8,178 (63.7)	9,061 (64.6)	0.126	8,704 (64.3)	8,535 (64.0)	0.693
Residential area (metropolitan)	14,621 (54.4)	4,168 (32.5)	10,453 (74.5)	< 0.001	6,778 (50.1)	7,843 (58.9)	< 0.001
Location of arrest (public place)	4,928 (18.3)	2,333 (18.2)	2,595 (18.5)	0.488	2,488 (18.4)	2,440 (18.3)	0.893
Witnessed arrest	13,689 (51.0)	6,547 (51.0)	7,142 (50.9)	0.895	6,863 (50.7)	6,826 (51.2)	0.376
Prehospital shockable ECG	4,848 (18.0)	2,213 (17.2)	2,635 (18.8)	< 0.001	2,416 (17.8)	2,432 (18.3)	0.385
Dispatcher recognition	19,450 (72.4)	9,236 (71.9)	10,214 (72.8)	0.109	9,868 (72.9)	9,582 (71.9)	0.075
Bystander CPR	17,041 (63.4)	8,364 (65.1)	8,677 (61.9)	< 0.001	8,790 (64.9)	8,251 (61.9)	< 0.001
Prehospital defibrillation	6,577 (24.5)	3,049 (23.7)	3,528 (25.1)	0.008	3,311 (24.5)	3,266 (24.5)	0.914
EMS RTI (min)	6 (5–8)	7 (5–9)	6 (5–8)	< 0.001	6 (5–8)	6 (5–8)	< 0.001
Time interval between EMS units (min)	4 (2–8)	5 (2–8)	4 (2–7)	< 0.001	4 (2–8)	4 (2–7)	< 0.001
EMS STI (min)	15 (12–21)	16 (12–22)	15 (12–19)	< 0.001	15 (11–20)	16 (12–21)	< 0.001
EMS TTI (min)	6 (4–9)	6 (4–9)	6 (4–8)	< 0.001	6 (4–9)	6 (4–8)	< 0.001
EMS resuscitation				< 0.001			< 0.001
Advanced airway management	22,310 (83.0)	10,215 (79.6)	12,095 (86.2)		10,625 (78.5)	11,685 (87.7)	
Intravenous route access	16,082 (59.9)	6,793 (52.9)	9,289 (66.2)		7,014 (51.8)	9,068 (68.0)	
Intravenous medication administration	6,001 (22.3)	2,984 (23.2)	3,017 (21.5)		2,550 (18.8)	3,451 (25.9)	
ED level 1 or 2	19,823 (73.8)	9,170 (71.4)	10,653 (75.9)	< 0.001	10,051 (74.2)	9,772 (73.3)	0.095
Outcomes							
ROSC upon arrival at the ED	3,679 (13.7)	1,589 (12.4)	2,090 (14.9)	< 0.001	1,634 (12.1)	2,045 (15.3)	< 0.001
Survival to discharge	2,602 (9.7)	1,094 (8.5)	1,508 (10.7)	< 0.001	1,222 (9.0)	1,380 (10.4)	< 0.001
Good neurologic recovery	1,706 (6.3)	698 (5.4)	1,008 (7.2)	< 0.001	804 (5.9)	902 (6.8)	0.005

Values are presented as number (%) or median (interquartile range).
EMS, emergency medical services; EMT-I, emergency medical technician intermediate level; ECG, electrocardiogram; CPR, cardiopulmonary resuscitation; RTI, response time interval; STI, scene time interval; TTI, transport time interval; ED, emergency department; ROSC, return of spontaneous circulation.

Table 2. Multivariable logistic regression analysis by number or EMT-I proportion of first-contact EMS crews on clinical outcomes

Clinical outcome	Good neurologic recovery		Survival to discharge		Prehospital ROSC	
	Crude OR (95% CI)	Adjust OR (95% CI)	Crude OR (95% CI)	Adjust OR (95% CI)	Crude OR (95% CI)	Adjust OR (95% CI)
Three EMS providers (vs. two EMS providers)	1.34 (1.20–1.50)	1.23 (1.06–1.43)	1.28 (1.18–1.40)	1.18 (1.07–1.31)	1.34 (1.26–1.42)	1.29 (1.21–1.39)
EMT-I > 50% (vs. EMT-I ≤ 50%)	1.18 (1.02–1.37)	1.28 (1.17–1.40)	1.17 (1.05–1.31)	1.16 (1.08–1.25)	1.26 (1.12–1.42)	1.28 (1.17–1.40)

ORs were calculated after adjusting for age group, sex, public versus private location, metropolitan area, witness status, dispatcher recognition, bystander cardiopulmonary resuscitation, initial electrocardiogram rhythm, response time interval, time interval between EMS unit arrival, transport time interval, number and level of second-contact EMS crew, and level of emergency department.
EMT-I, emergency medical technician intermediate level; EMS, emergency medical services; ROSC, return of spontaneous circulation; OR, odds ratio; CI, confidence interval.

DISCUSSION

In this study, we analyzed the association between the number and level of first-contact EMS crews and survival outcomes in DDR-activated OHCA. Statistically significant differences were found for good neurologic recovery, survival to discharge, and prehospital ROSC among the high number of EMS providers and high EMT-I proportion crews for first-contact EMS units. In the interaction analysis, the effect of a high number of EMS providers was strengthened by a low EMT-I proportion.

These results can be explained by the influence of a single EMS team resuscitation during the entire DDR phase. Even if an emergency call is suspected to be an OHCA by the dispatcher and DDR is activated, practical resuscitation provided before the second-contact EMS crew arrives will be less effective than team-based resuscitation. The difference in CPR quality during that period would be strongly dependent on the number and level of EMS personnel, as found by Sun et al.[19] in a Taipei study. Although the

Table 3. Interaction analysis by EMT-I proportion across number of first-contact EMS crews and clinical outcomes

Clinical outcome	Adjusted odds ratio (95% confidence interval)		
	Good neurologic recovery	Survival to discharge	Prehospital ROSC
Three EMS providers (vs. two EMS providers)	1.16 (1.00–1.35)	1.11 (1.04–1.18)	1.09 (1.09–1.10)
EMT-I >50% (vs. EMT-I ≤50%)	1.10 (1.09–1.11)	1.13 (1.09–1.18)	1.35 (1.30–1.41)
No. of EMS providers × EMT-I ≤50%	1.26 (1.02–1.54)[a]	1.14 (1.00–1.29)	1.06 (0.98–1.13)

Odd ratios were calculated after adjusting for age group, sex, public versus private location, metropolitan area, witness status, dispatcher recognition, bystander cardiopulmonary resuscitation, initial electrocardiogram rhythm, response time interval, time interval between EMS unit arrival, transport time interval, number and level of second-contact EMS crew, and level of emergency department.
EMT-I, emergency medical technician intermediate level; EMS, emergency medical services; ROSC, return of spontaneous circulation.
[a]P-value for interaction effect <0.05.

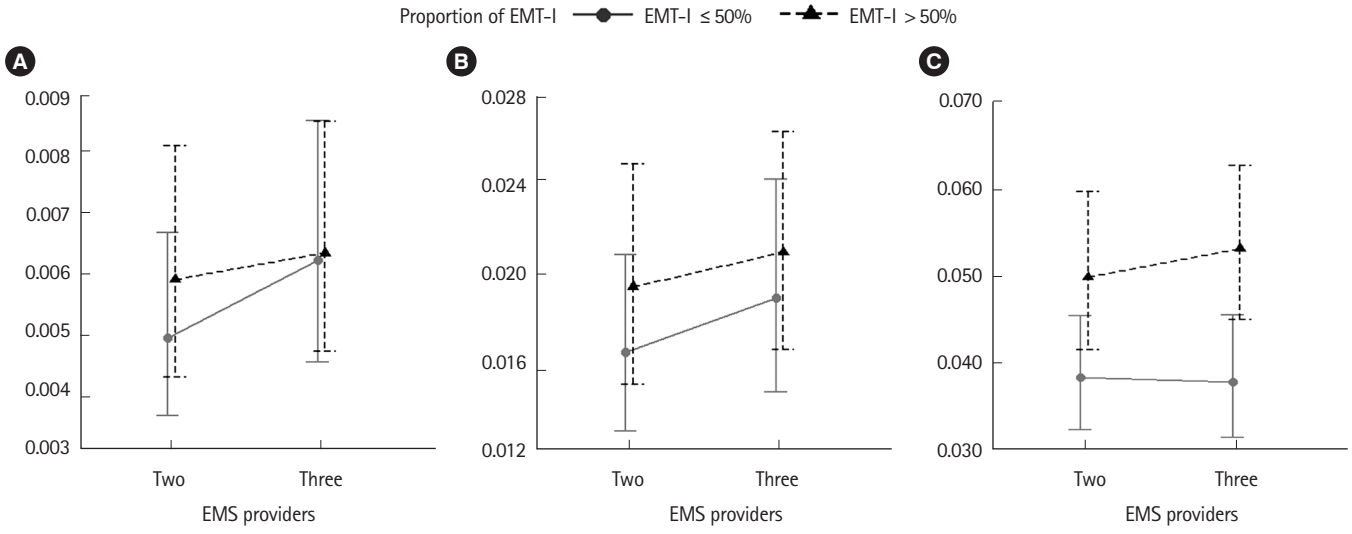

Fig. 3. Interaction plot by emergency medical technician intermediate level (EMT-I) proportion across number of first-contact emergency medical services (EMS) crews and clinical outcomes. (A) Good neurologic recovery, (B) survival to discharge, and (C) prehospital return of spontaneous circulation.

total number of EMTs is thought to be sufficient in a DDR setting, during the early phase of field resuscitation prior to arrival of the second crew, the number of EMTs and their level of training may be critical.

Significant probabilities for favorable clinical outcomes have been found among crews with higher proportions of higher level EMTs (EMT-I). ACLS procedures, such as advanced airway management or epinephrine delivery, had potential associations with OHCA outcomes, especially short-term survival and prehospital ROSC.[31,32] In Korea, EMT-I can perform ACLS procedures at the scene, and high EMT-I proportion crews could deliver higher provision rates (Table 1).

We assumed that the magnitude of the effect of the number of first-contact EMS crew members would be strengthened by a higher proportion of EMT-I crew members. However, the magnitude of the difference between two and three EMS personnel in first-contact EMS unit increased according to a lower proportion of EMT-I, which suggests that the lower the level of the individuals in the team, the more effective the additional personnel are for prehospital resuscitation. Thus, it may be beneficial to increase EMS personnel, especially in regions with few high-level EMTs.

Based on our results, policy makers should consider allocating more human resources, including number and level of EMS providers, to regions where second-contact EMS units cannot arrive to the scene fast enough. Our findings indicate that the first-contact EMS unit responding to an OHCA should add additional crew as the first priority in conditions where there are only two EMT-Bs allocated. Similarly, a further interaction analysis by number of second-contact EMS crews showed that the effect of three members in first-contact EMS crew was strengthened when there were fewer EMS personnel in the second-contact ambulance (Supplementary Table 1).

Reducing the response time of a relatively higher grade of EMS units would be important. Because it is mostly impossible to allocate the entire EMS unit to a maximum number and level, a dispatch protocol assigning suspected OHCA cases to a specific EMS

unit can be considered. Currently, the Korean EMS system is operated in a nationwide universal dispatch protocol with DDR activation for suspected OHCA, in which the nearest EMS unit is sent as quickly as possible without consideration of the team characteristics. Table 1 showed that there is no significant difference in proportion of dispatcher recognition between the team characteristics.

The Korean government has been working to cultivate EMS staffing for many years, and the proportion of EMT-I and number of three-member EMS crews among first-contact EMS units is constantly increasing (Supplementary Fig. 1). It may be appropriate to consider categorizing EMS units according to their CPR performance and give priority to suspected OHCA cases. EMS units with more EMS providers and higher proportions of EMT-I should be on standby, and the other EMS units should have priority over dispatch to clear non-OHCA cases or as second-contact EMS crews in DDRs. The accuracy of dispatcher recognition of OHCA would also be important to evaluate.

This study has several limitations. First, main exposure was defined according to the number and certification level of the EMS crew, not by individual performance. To measure each crew's detailed resuscitative procedures, feedback devices and video records are needed, which were limited in our data sources. Similarly, quality of CPR and early defibrillation cannot be measured. Second, the number of crews in an EMS unit and the types of certification levels varies according to country, which limits the generalizability of the study. Third, the Korean EMS system adopted the "scoop and run" model, in which the scene resuscitation time is usually short, which affects the results. Findings are likely different for other countries that allow resuscitation termination at the scene. For generalizability, further investigation across various environments is needed. Last, this study is a retrospective observational cohort study from which causality cannot be determined, and the data may contain significant potential uncontrolled biases. Additionally, unmeasured confounders could not be collected, such as team dynamics among EMS personnel.

For adult medical OHCA treated by a dual dispatch EMS response system, the number and level of first-contact EMS crew is associated with neurologic recovery and survival outcomes. These study findings may serve as a basis of policy development for EMS dispatch protocols and allocation of emergency resources.

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Interaction analysis by proportion of number of second-contact EMS crews across number of first-contact EMS crews and clinical outcomes

Supplementary Fig. 1. Yearly trend in first-contact emergency medical services (EMS) crew according to the study group.
Supplementary materials are available at https://doi.org/10.15441/ceem.22.205.

CONFLICT OF INTEREST

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

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AUTHOR CONTRIBUTIONS

Conceptualization: YSK, KHK; Data curation: KJS, SDS; Formal analysis: YSK, KHK; Investigation: YSK, KHK; Methodology: JHP, KJK; Project administration: KJS, SDS; Resources: KJS, SDS; Software: YSK, KHK; Supervision: JHP; Validation: JHP; Visualization: YSK, KHK; Writing–original draft: YSK, KHK; Writing–review & editing: all authors.
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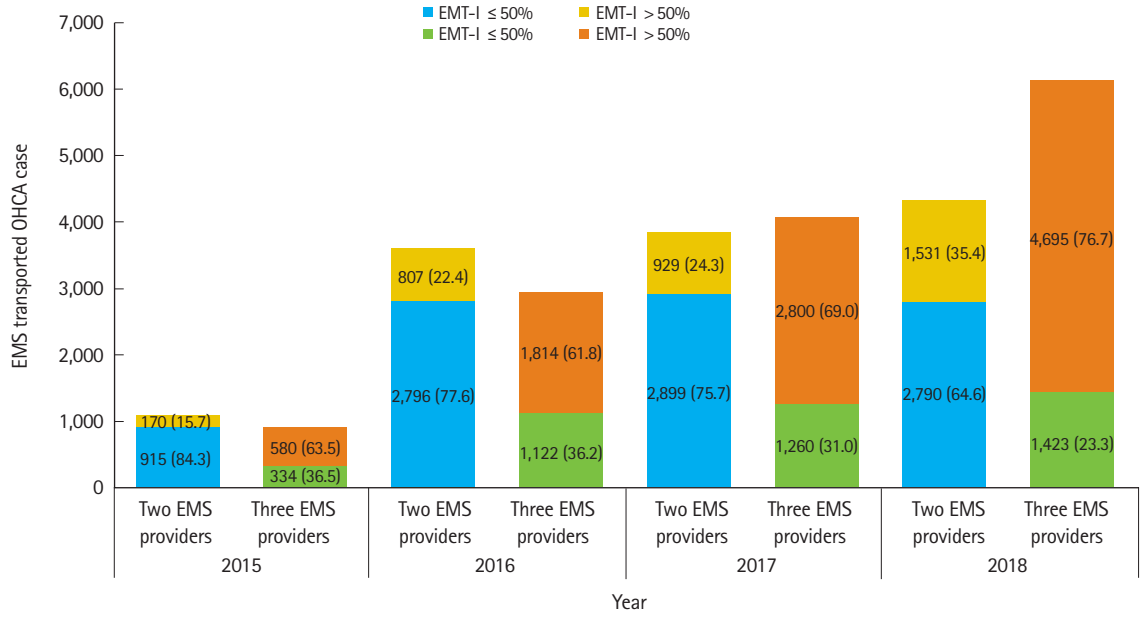
Supplementary Table1. Interaction analysis by proportion of number of second-contact EMS crews across number of first-contact EMS crews and clinical outcomes

Variable	Adjusted odds ratio (95% confidence interval)		
	Good neurologic recovery	Survival to discharge	Prehospital ROSC
Three EMS providers in second-contact EMS			
Three EMS providers in first-contact EMS	1.07 (1.00–1.15)	1.12 (1.05–1.20)	1.18 (1.12–1.26)
Two EMS providers in first-contact EMS	1.00	1.00	1.00
Two EMS providers in second-contact EMS			
Three EMS providers in first-contact EMS	1.36 (1.19–1.54)[a]	1.22 (1.13–1.31)	1.35 (1.26–1.46)[a]
Two EMS providers in first-contact EMS	1.00	1.00	1.00

Odd ratios were calculated adjusting for age group, gender, public place, metropolitan area, witness status, dispatcher recognition, bystander cardiopulmonary resuscitation, initial electrocardiogram rhythm, response time interval, time interval between EMS units arrival, transport time interval, number and level of second contact EMS crew, and level of emergency department.

EMS, emergency medical services; ROSC, return of spontaneous circulation.

[a]P-value for interaction effect below 0.05.



Supplementary Fig. 1. Yearly trend in first contact emergency medical services (EMS) crew according to the study group. Values on the bar are presented as number (%). OHCA, out-of-hospital cardiac arrest; EMT-I, emergency medical technician intermediate level.

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Original Article

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Association between prehospital recognition of acute myocardial infarction and length of stay in the emergency department

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Objective This study aimed to evaluate the association between prehospital recognition of acute myocardial infarction (AMI) and length of stay (LOS) in the emergency department (ED) of emergency medical service (EMS)-transported AMI patients.

Methods A multicenter retrospective observational study was conducted using prehospital and hospital data from three tertiary emergency departments. Patients diagnosed with AMI between January 2015 and December 2018 were enrolled. Study groups were categorized according to prehospital recognition and prehospital 12-lead electrocardiography (ECG) into three groups based on an EMS cardiovascular registry: group A, no prehospital recognition (reference group); group B, prehospital recognition without 12-lead ECG; and group C, prehospital recognition with 12-lead ECG. The primary outcome was an ED LOS of less than 4 hours.

Results Among 1,237 study participants, 722 (58.4%) were in group A, 325 (26.3%) were in group B, and 190 (15.4%) were in group C. Multivariable logistic regression showed that groups B and C had a higher likelihood of a short ED LOS (adjusted odds ratio [95% confidence interval]: group B, 1.64 [1.21–2.22] and group C, 1.88 [1.30–2.71]) than group A. There was no significant difference in ED LOS according to whether prehospital 12-lead ECG was conducted.

Conclusion Prehospital recognition of AMI by EMS personnel, with or without 12-lead ECG, was associated with a short ED LOS.

Keywords Emergency medical services; Myocardial infarct; Length of stay

Capsule Summary

What is already known

Emergency department length of stay affects clinical outcomes in patients with acute myocardial infarction. Emergency medical service providers can recognize potential acute myocardial infarction in the prehospital phase.

What is new in the current study

Prehospital recognition of acute myocardial infarction by emergency medical service providers is associated with a short length of stay in the emergency department.

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INTRODUCTION

Acute myocardial infarction (AMI), including both ST elevation myocardial infarction (STEMI) and non-STEMI, is a common cardiac emergency condition and is associated with a high risk of serious morbidities and mortality.[1] Although the incidence of AMI has decreased significantly in recent decades,[2] AMI is still a major global health burden, with AMI associated with an increased number of years with disability.[3] In Korea, AMI is the second leading cause of death, with 60 deaths due to AMI among every 100,000 people.[4] AMI has also been demonstrated to have a high economic cost.[5]

Shortening the time delay in diagnosis and treatment of AMI is crucial for achieving optimal clinical outcomes.[6,7] The American College of Cardiology and American Heart Association proposed an ideal time window for intervention in STEMI patients,[8] and recommended that suspected AMI patients receive emergency medical service (EMS) to shorten the time delay.[9] The length of stay (LOS) in the emergency department (ED), as an index of time delay, was found to be associated with clinical outcomes in time-sensitive conditions, including AMI.[10,11] ED routine issues, including diagnostic difficulties, have been demonstrated to contribute to in-hospital delays.[12]

EMS management of AMI is important because early assessment, treatment, and expedited communication with the receiving hospital are associated with improved patient outcomes.[13] The ED bypass program based on early recognition of AMI by EMS was demonstrated to have a significant association with survival outcome in a STEMI cohort.[14] Additionally, Bright et al.[15] reported high accuracy among EMS personnel in the prehospital diagnosis of AMI. Prehospital 12-lead electrocardiography (ECG) by EMS personnel is strongly recommended and implemented worldwide.[16] Hutchison et al.[17] reported that the time to intervention was greatly decreased with clinical pathway activation based on prehospital 12-lead ECG findings. Prehospital 12-lead ECG was also found to help the ED achieve the ideal time window for intervention and was therefore associated with a lower mortality rate in AMI patients.[18]

The effect of prehospital recognition on the ED process has not been well evaluated for patients with AMI. We hypothesized that prehospital recognition of AMI would reduce the ED LOS and that prehospital 12-lead ECG would strengthen this association. The purpose of this study was therefore to evaluate the association between prehospital recognition with or without 12-lead ECG and ED LOS in EMS-transported AMI patients.

METHODS

Ethical statements

This study complies with the Declaration of Helsinki, and its protocol was approved by the Institutional Review Board of Seoul National University Hospital (No. 2006-004-1128). The Institutional Review Board waived the requirement for informed consent due to the retrospective nature of the study.

Study design and data source

This study was a cross-sectional, retrospective, observational study based on an integrated database including data from three academic tertiary emergency departments from January 2015 to December 2018. Data were obtained from three sources: EMS ambulance run-sheets, EMS cardiovascular registry, and hospital administrative databases. EMS time variables, chief complaints, and vital signs measured at the scene are collected by EMS personnel on an EMS run-sheet for all EMS-transported patients. The EMS cardiovascular registry contains information about past medical history, prehospital sublingual nitroglycerine administration, 12-lead ECG at the scene, prenotification of the receiving hospital, and presumed acute cardiovascular disease for highly suspicious cases. Hospital administrative databases contain information about the clinical course, including the time of visit, physiologic status at triage, diagnosis at the ED or hospital discharge, time of admission or discharge, and status at discharge. We integrated data from the three sources using a common deidentified key to produce a comprehensive clinical dataset.

Study setting

The Korean EMS, which is a public health service, is operated by the National Fire Agency and includes 17 provincial headquarters with approximately 200 fire stations, 1,000 EMS agencies, and 8,400 EMS personnel. Ambulances assigned to regional EMS agencies are dispatched for emergency calls. Korean EMS personnel have certification levels ranging from basic to intermediate, including intravenous fluid administration and advanced airway management under direct medical oversight by doctors. A 6-month curriculum is provided to all EMS providers at the Fire Service Academy, with a minimum of 1 month of first aid practice including 12-lead ECG interpretation in the field. Act 119 regarding the rescue and EMS mandates that patient information be input into structured sheets (EMS run-sheets) by EMS personnel immediately after transportation.[19] An additional cardiovascular registry needs to be filled out if a patient complains of chest pain, respiratory difficulty, or syncope, or if acute cardiovascular disease is suspected by EMS personnel. EMS personnel are instructed to per-

form 12-lead ECG if an ECG device is available, and the patient is suspected of having acute cardiovascular disease and to transport the patient to the nearest at least level 2 ED. Sublingual nitroglycerin can be attempted at most three times per 5-minute intervals under direct medical oversight if no contraindications are present.

In Korea, EDs are categorized into three levels by the Ministry of Health and Welfare: level 1 EDs (n = 36), where 24/7 emergency care for critically ill emergency patients is provided by emergency physicians; level 2 EDs (n = 119), where emergency physicians provide high-acuity emergency care for emergency patients; and level 3 EDs (n = 261), where general physicians provide low-acuity emergency care for patients. All EDs in Korea undergo an annual nationwide functional performance evaluation by the Ministry of Health and Welfare. Level 1 and 2 EDs have a cardiology intervention team, which is headed by an emergency physician, and general acute cardiac care is performed following international standard guidelines. Emergency physicians are responsible for making critical decisions for patient care.[20,21]

After EMS personnel deliver on-scene clinical information to the triage nurse at the entrance of the ED, all patients are assessed and categorized into one of five levels according to the urgency of emergency medical care. Patients suspected of AMI undergo urgent ECG, and the emergency physician can directly notify the on-call intervention team regarding suspected STEMI (STEMI critical pathway). Otherwise, after full evaluation, including cardiac biomarker tests, an assigned emergency physician will consult an on-duty cardiologist regarding hospitalization. Since ED care performance for AMI patients is evaluated by the government, reducing the ED LOS is strongly recommended.

Study population

EMS-assessed and transported adult nontraumatic AMI patients seen from January 2015 to December 2018 who were admitted following their ED visit were enrolled. We excluded patients transported between hospitals, patients with cardiac arrest, discharged patients, and patients with missing outcomes. Patients were identified according to International Statistical Classification of Diseases 10th Revision (ICD-10) diagnostic codes of I-210 and I-219, which indicate AMI. The ED administrative database has two types of primary diagnostic codes: the final diagnostic codes at ED discharge and at hospital discharge. A patient was considered positive for AMI if a confirmative diagnostic code was found at any point in the discharge record. Coronary angiography reports were not taken into consideration to confirm diagnosis, as the goal of this study was to evaluate the association between prehospital recognition of AMI and ED LOS.

Outcome measures

The primary outcome was the ED LOS, defined as the time interval from ED arrival to ED departure due to admission to the floor; this was collected from the hospital administrative database. Four hours was defined as a short ED LOS as this time interval has been used as the target in previous studies.[22,23] Inpatient (IP) LOS, which is a clinical outcome indicator,[24] was used as the secondary outcome, and the median value was selected for reference. Survival to discharge, which was evaluated at the point of hospital discharge and collected from the administrative database, was additionally used as the tertiary outcome.

Variables and measurements

The main exposures were prehospital recognition of acute cardiovascular disease by EMS personnel (prehospital recognition) and prehospital 12-lead ECG. Prehospital recognition was defined as positive if EMS personnel entered the patient with presumed acute cardiovascular disease into the cardiovascular registry. Whether 12-lead ECG was conducted at the scene was assessed in the same way. The study population was categorized into three groups: group A, no prehospital recognition (reference group); group B, prehospital recognition without 12-lead ECG; and group C, prehospital recognition with prehospital 12-lead ECG.

The following demographic and clinical data were collected and categorized: age (under 49, 50–59, 60–69, 70–79, and over 80 years old), sex, ED visit time (morning, evening, or night), weekend presentation, season of the ED visit, chief complaint (chest pain, atypical coronary symptoms, including dyspnea, syncope, palpitation, epigastric pain, and chest burning), past heart disease history, prehospital shock status (systolic blood pressure under 90 mmHg), prehospital abnormal heart rate (heart rate over 100 beats/min and under 60 beats/min), prehospital alertness, ST-segment abnormality in prehospital 12-lead ECG, prehospital sublingual nitroglycerin administration, receiving hospital notification before ED arrival, shock status at ED triage, abnormal heart rate at ED triage, direct transport to the angiography room with confirmation of ST-segment elevation in the initial ECG examination (STEMI critical pathway), and intensive care unit (ICU) admission (including coronary unit). Median imputation was conducted for missing values for age and vital signs, which occurred in less than 20% of the study population.

Statistical analysis

A descriptive analysis was performed to analyze the distributions of the demographic and clinical data of the study population. Chi-squared tests for categorical variables and Wilcoxon rank-sum tests for continuous variables were used. To determine the associ-

ations between prehospital recognition with and without 12-lead ECG and outcomes, adjusted odds ratios (AORs) with 95% confidence intervals (CIs) were calculated using a multivariable logistic regression analysis with group A as the reference. We adjusted for age group, sex, past medical history of heart disease, chief complaint of chest pain and atypical coronary symptoms, prehospital shock, prehospital alertness, and time, weekend, and season of the ED visit. To determine the effectiveness of 12-lead ECG on prehospital recognition, AORs and 95% CIs were recalculated with the aforementioned regression model with group B as a reference.

To evaluate changes in effect size according to the characteristics of the patients, sensitivity analyses were performed. Since one of the main variables affecting ED LOS is severity, the subgroup of patients admitted to the ICU was extracted, and the same statistical analyses were performed. We also conducted additional subgroup analysis for non-STEMI patients considering that the STEMI critical pathway could significantly affect the results. All statistical analyses were performed using SAS ver. 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Demographic findings

Among 4,988 patients diagnosed with AMI from January 2015 to December 2018, 1,237 patients were included in the final analysis. We excluded 22 injured patients, five pediatric patients, 388 patients with symptoms occurring for more than a week, 3,114 non-EMS users, 87 patients transported between hospitals, 89 patients with out-of-hospital and in-hospital cardiac arrest, and 56 patients with no outcome data at discharge (Fig. 1).

Table 1 presents demographic and clinical data according to study group. Patients in group C were more likely to be male and less likely to visit the ED at night (11 PM–7 AM) or in the summer. Patients in group A had lower proportions of typical coronary symptoms, past medical history of heart disease, prehospital alertness, prehospital sublingual nitroglycerin administration, and prenotification of the receiving hospital. Group A had a lower proportion of STEMI critical pathway patients than groups B and C: 12.0% in group A, 25.2% in group B, and 29.5% in group C. The main outcomes showed significant differences according to study group: the percentages of patients with a short ED LOS and short IP LOS were 41.7% and 40.0% in group A, 57.8% and 52.3% in group B, and 60.5% and 58.4% in group C, respectively (Table 1).

Main analysis

In multivariable logistic regression analysis, statistically significant differences in ED LOS were found for groups B and C compared to group A (ED LOS less than 4 hours, AOR [95% CI]: 1.64 [1.21–2.22] in group B and 1.88 [1.30–2.71] in group C). There was no significant difference in IP LOS or survival to discharge (IP

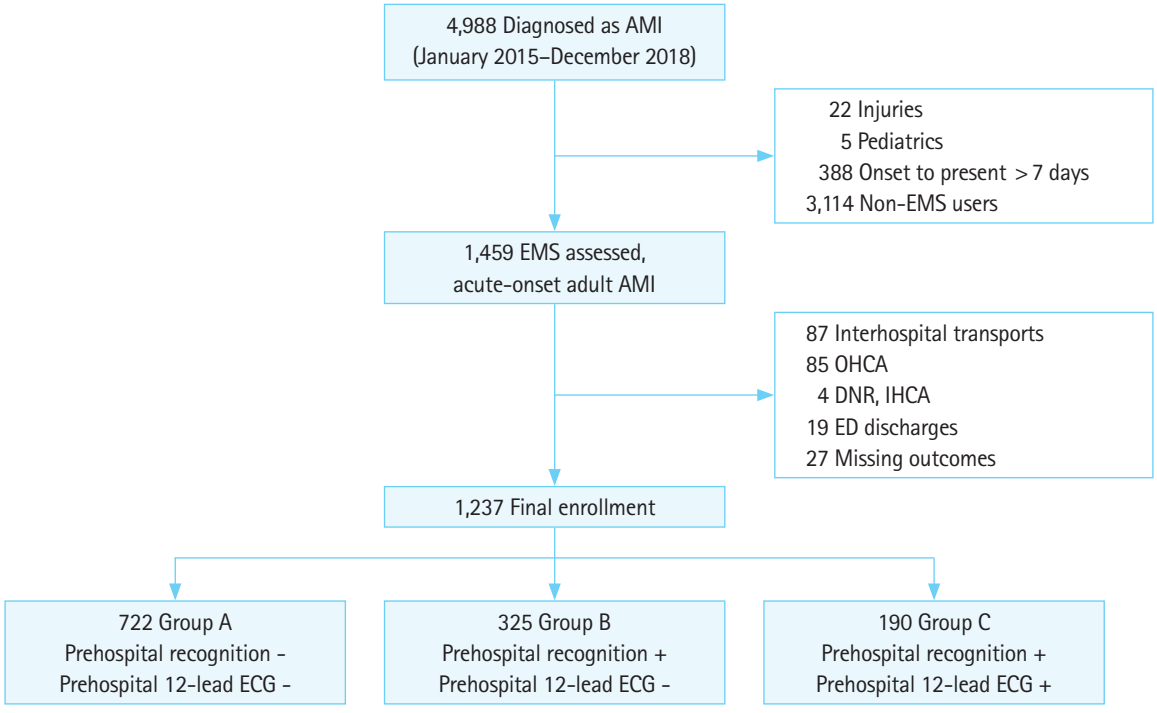

Fig. 1. Patient flow. AMI, acute myocardial infarction; EMS, emergency medical service; OHCA, out-of-hospital cardiac arrest; DNR, do not resuscitate; IHCA, in-hospital cardiac arrest; ED, emergency department; ECG, electrocardiography.

Table 1. Demographics and clinical findings according to study group

Characteristic	Total	Group			P-value
		A	B	C	
Total	1,237 (100)	722 (58.4)	325 (26.3)	190 (15.4)	
Age (yr)	71 (61–78)	73 (62–80)	68 (59–76)	68 (58–76)	< 0.01
Age group (yr)					0.04
≤ 49	37 (3.0)	17 (2.4)	10 (3.1)	10 (5.3)	
50–59	384 (31.0)	204 (28.3)	117 (36.0)	63 (33.2)	
60–69	563 (45.5)	325 (45.0)	147 (45.2)	91 (47.9)	
70–79	215 (17.4)	149 (20.6)	41 (12.6)	25 (13.2)	
≥ 80	38 (3.1)	27 (3.7)	10 (3.1)	1 (0.5)	
Male sex	855 (69.1)	480 (66.5)	228 (70.2)	147 (77.4)	0.02
ED visit time					< 0.01
7 AM–3 PM	526 (42.5)	313 (43.4)	128 (39.4)	85 (44.7)	
3 PM–11 PM	393 (31.8)	225 (31.2)	98 (30.2)	70 (36.8)	
11 PM–7 AM	318 (25.7)	184 (25.5)	99 (30.5)	35 (18.4)	
Weekend	343 (27.7)	202 (28.0)	88 (27.1)	53 (27.9)	0.52
Season					< 0.01
Spring	302 (24.4)	172 (23.8)	92 (28.3)	38 (20.0)	
Summer	288 (23.3)	173 (24.0)	74 (22.8)	41 (21.6)	
Autumn	335 (27.1)	185 (25.6)	84 (25.8)	66 (34.7)	
Winter	312 (25.2)	192 (26.6)	75 (23.1)	45 (23.7)	
Chief complaint					< 0.01
Chest pain	731 (59.1)	295 (40.9)	276 (84.9)	160 (84.2)	
Atypical coronary symptom	253 (20.5)	199 (27.6)	32 (9.8)	22 (11.6)	
Past heart disease history	443 (35.8)	211 (29.2)	139 (42.8)	93 (48.9)	< 0.01
Prehospital variable					
Hypotension (< 90 mmHg)	74 (6.0)	35 (4.8)	26 (8.0)	13 (6.8)	0.33
Abnormal heart rate					< 0.01
Bradycardia (< 60 beats/min)	137 (11.1)	67 (9.3)	42 (12.9)	28 (14.7)	
Tachycardia (> 100 beats/min)	308 (24.9)	204 (28.3)	69 (21.2)	35 (18.4)	
Alertness	1,164 (94.1)	665 (92.1)	312 (96.0)	187 (98.4)	< 0.01
EMS 12-lead ECG with ST change	114 (9.2)	9 (1.2)	0 (0)	105 (55.3)	< 0.01
Nitroglycerin	94 (7.6)	15 (2.1)	46 (14.2)	33 (17.4)	< 0.01
Notification of receiving hospital	454 (36.7)	153 (21.2)	162 (49.8)	139 (73.2)	< 0.01
ED variable					
Hypotension at ED triage (< 90 mmHg)	76 (6.1)	55 (7.6)	15 (4.6)	6 (3.2)	< 0.01
Abnormal heart rate at ED triage					0.06
Bradycardia (< 60 beats/min)	247 (20.0)	126 (17.5)	82 (25.2)	39 (20.5)	
Tachycardia (> 100 beats/min)	214 (17.3)	150 (20.8)	42 (12.9)	22 (11.6)	
STEMI critical pathway	225 (18.2)	87 (12.0)	82 (25.2)	56 (29.5)	< 0.01
ED LOS (hr)	4.3 (1.2–8.4)	5.1 (1.7–9.4)	2.5 (0.9–7.3)	1.8 (0.9–6.6)	< 0.01
Hospital LOS (day)	4.4 (2.9–8.5)	5.0 (3.0–10.4)	4.0 (2.7–6.6)	3.9 (2.8–5.9)	< 0.01
Main outcome					
ED LOS (< 4 hr)	604 (48.8)	301 (41.7)	188 (57.8)	115 (60.5)	< 0.01
Inpatient LOS (< 4 day)	570 (46.1)	289 (40.0)	170 (52.3)	111 (58.4)	< 0.01
Clinical outcome					
Intensive care unit admission	542 (43.8)	288 (39.9)	151 (46.5)	103 (54.2)	< 0.01
Survival to discharge	1,135 (91.8)	645 (89.3)	309 (95.1)	181 (95.3)	< 0.01

Values are presented as number (%) or median (interquartile range).
ED, emergency department; EMS, emergency medical service; ECG, electrocardiography; STEMI, ST elevation myocardial infarction; LOS, length of stay.

LOS less than 4 days, AOR [95% CI]: 1.02 [0.75–1.37] in group B and 1.25 [0.87–1.79] in group C; survival to discharge, AOR [95% CI]: 1.14 (0.60–2.14) in group B and 1.20 [0.55–2.62] in group C) (Table 2). In multivariable linear regression analysis for ED LOS,

Table 2. Univariable and multivariable logistic regression by prehospital recognition with or without 12-lead electrocardiography

Outcome	No. (%)	Univariable analysis	Multivariable analysis[a]	
		OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)
ED LOS < 4 hr				
Group A	301 (41.7)	1.00	1.00	NA
Group B	188 (57.8)	1.92 (1.47–2.50)	1.64 (1.21–2.22)	1.00
Group C	115 (60.5)	2.15 (1.55–2.97)	1.88 (1.30–2.71)	1.14 (0.78–1.68)
Inpatient LOS < 4 day				
Group A	289 (40.0)	1.00	1.00	NA
Group B	170 (52.3)	1.64 (1.26–2.14)	1.02 (0.75–1.37)	1.00
Group C	111 (58.4)	2.11 (1.52–2.91)	1.25 (0.87–1.79)	1.23 (0.84–1.79)
Survival to discharge				
Group A	645 (89.3)	1.00	1.00	NA
Group B	309 (95.1)	2.31 (1.32–4.02)	1.14 (0.60–2.14)	1.00
Group C	181 (95.3)	2.40 (1.18–4.88)	1.20 (0.55–2.62)	1.05 (0.44–2.51)

The number of patients for groups A, B, and C were 722, 325, and 190, respectively. The multivariable model was adjusted for age group, sex, past heart disease history, chief complaint, prehospital shock, prehospital alertness, time of visit, weekend, and season.
OR, odds ratio; CI, confidence interval; ED, emergency department; LOS, length of stay; NA, not applicable.
[a]ORs were calculated with the same models with different references.

Table 3. Univariable and multivariable logistic regression by prehospital recognition with or without 12-lead electrocardiography in patients admitted to the intensive care unit

Outcome	No. (%)	Univariable analysis	Multivariable analysis[a]	
		OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)
ED LOS < 4 hr				
Group A	147 (51.0)	1.00	1.00	NA
Group B	104 (68.9)	2.12 (1.40–3.21)	1.85 (1.15–2.97)	1.00
Group C	69 (67.0)	1.95 (1.22–3.12)	1.77 (1.02–3.06)	0.96 (0.54–1.70)
Inpatient LOS < 4 day				
Group A	111 (38.5)	1.00	1.00	NA
Group B	67 (44.4)	1.27 (0.85–1.90)	0.95 (0.60–1.50)	1.00
Group C	56 (54.4)	1.90 (1.21–2.99)	1.35 (0.80–2.28)	1.42 (0.83–2.41)
Survival to discharge				
Group A	253 (87.8)	1.00	1.00	NA
Group B	141 (93.4)	0.51 (0.25–1.07)	0.85 (0.36–2.00)	1.00
Group C	97 (94.2)	0.45 (0.18–1.10)	0.83 (0.29–2.38)	0.97 (0.31–3.03)

The number of patients for groups A, B, and C were 288, 151, and 103, respectively. The multivariable model was adjusted for age group, sex, past heart disease history, chief complaint, prehospital shock, prehospital alertness, time of visit, weekend, and season.
OR, odds ratio; CI, confidence interval; ED, emergency department; LOS, length of stay; NA, not applicable.
[a]ORs were calculated with the same models with different references.

the coefficient for regression of the study group (reference, group A) was calculated to be -1.782 ($P < 0.01$).

In sensitivity analysis for patients admitted to the ICU, similar and statistically significant associations were found (ED LOS less than 4 hours, AOR [95% CI]: 1.85 [1.15–2.97] in group B and 1.77 [1.02–3.06] in group C) (Table 3). A similar trend was demonstrated for non-STEMI patients (ED LOS less than 4 hours, AOR [95% CI]: 1.46 [1.03–2.06] in group B and 1.55 [1.02–2.37] in group C) (Table 4).

DISCUSSION

In EMS-transported AMI patients admitted to the ED, prehospital recognition was found to be associated with a short ED LOS. There was no statistically significant difference according to prehospital 12-lead ECG. IP LOS and survival to discharge had no significant association with prehospital recognition with or without 12-lead ECG. The same trends were sustained and statistically significant in patients admitted to the ICU and in non-STEMI patients. Careful prehospital evaluation for AMI by EMS personnel should be

Table 4. Univariable and multivariable logistic regression by prehospital recognition with or without 12-lead electrocardiography in non-ST-elevation myocardial infarction patients

Outcome	No. (%)	Univariable analysis	Multivariable analysis[a]	
		OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)
ED LOS < 4 hr				
Group A	214 (33.7)	1.00	1.00	NA
Group B	106 (43.6)	1.52 (1.13–2.06)	1.46 (1.03–2.06)	1.00
Group C	59 (44.0)	1.55 (1.06–2.26)	1.55 (1.02–2.37)	1.07 (0.68–1.66)
Inpatient LOS < 4 day				
Group A	249 (39.2)	1.00	1.00	NA
Group B	132 (54.3)	1.84 (1.37–2.49)	1.12 (0.80–1.57)	1.00
Group C	73 (54.5)	1.86 (1.27–2.70)	1.07 (0.70–1.63)	0.95 (0.61–1.49)
Survival to discharge				
Group A	564 (88.8)	1.00	1.00	NA
Group B	229 (94.2)	2.06 (1.14–3.73)	1.05 (0.53–2.09)	1.00
Group C	126 (94.0)	1.98 (0.93–4.22)	0.98 (0.42–2.29)	0.93 (0.36–2.37)

The number of patients for groups A, B, and C were 635, 243, and 134, respectively. The multivariable model was adjusted for age group, sex, past heart disease history, chief complaint, prehospital shock, prehospital alertness, time of visit, weekend, and season.
OR, odds ratio; CI, confidence interval; ED, emergency department; LOS, length of stay; NA, not applicable.
[a]ORs were calculated with the same models with different references.

emphasized to improve the clinical course of these patients.

Prehospital recognition of AMI is associated with a higher probability of notification of the receiving hospital. This should ideally result in activation of the AMI practice process in the hospital, which could shorten ED LOS. We found that there were more AMI patients with a short ED LOS (under 4 hours) when the hospital received notification of an AMI during the prehospital phase, even after excluding STEMI cases, then when no prenotification was received (42.1% vs 35.0%, respectively).

In the prehospital phase of AMI, patients present with more pronounced symptoms, and recognition of these symptoms can optimize patient assessment and triage.[25] With sufficient experience and focused education, EMS personnel can identify high-risk features that indicate the possibility of acute cardiovascular disease.[26] A detailed history taken at the scene can provide meaningful information to ED staff, who can use this information to direct the assessments performed, thus accelerating the clinical process. However, the delivery of misleading information may interfere with the direction of the assessments performed and thus the clinical course of the patient. Considering that communication barriers extend ED LOS, the first impression of EMS personnel can influence ED staff.[27]

Additionally, the presence or absence of a sublingual nitroglycerin effect on chest pain is an important diagnostic predictor.[28] EMS personnel can evaluate this effect more clearly at the scene when chest pain has not yet subsided, as chest pain often improves spontaneously and changes to ambiguous symptoms at ED arrival. In such situations, ED LOS can be prolonged, as the application of proper diagnostic algorithms to reach the right diagnosis is limited.[29] In the prehospital recognition group, the number of sublingual nitroglycerin administrations was seven to eight times higher than in the other groups (Table 1).

In this study, prehospital recognition of AMI by EMS personnel was documented in the official registry. There is no detailed protocol about when EMS personnel should consider the patient to have suspected acute cardiovascular disease, but typical questions should be asked to complete the cardiovascular registry questions, such as the location and intensity of pain, whether the pain is radiating, and aggravating and relieving factors. The National Fire Agency provides a routine continuing education course for EMS personnel, including information on the presentations of acute critical illnesses such as AMI. EMS personnel are likely able to differentiate the possibility of AMI on the basis of complaints, past medical history, and vital signs. Sixty percent of the total patients had chest pain, but 40% of them were not recognized as having acute cardiovascular disease (Table 1), so we hypothesize that unmeasured factors affected EMS personnel assessments. Recognition of the overlooked AMI population is crucial to improve the clinical process.

ED LOS has been considered an indicator of the ED care process in previous studies.[30-32] Unlike cardiac arrest or trauma, in which prehospital resuscitation determines the status of patients at the ED entrance level, the role of EMS personnel in STEMI usually focuses on 12-lead electrocardiogram interpretation and ED bypass.[8] Considering that overcrowding and limited resources are major challenges to ED AMI diagnostic performance,[33] detailed

and accurate prehospital assessments are helpful from the beginning of ED care. Additionally, prenotification of receiving hospitals affects the ED care process. In the study group with prehospital recognition, a higher proportion of the patients' hospitals were notified before ED arrival, even when no 12-lead ECG results were available.

Condition severity has been demonstrated to be associated with ED LOS.[34] Sensitivity analysis of patients admitted to the ICU was performed to correct for unmeasured biases, such as a delay in admission based on nonmedical issues. Similar trends with statistical significance were found regarding the outcomes of patients admitted to the ICU and non-STEMI patients. Therefore, we highly recommend that EMS personnel assess the probability of AMI at the scene, especially in patients with indications of high condition severity, even without evidence of STEMI.

Our results indicate that prehospital EMS assessment could be beneficial for the ED care process, but the effect of prehospital recognition on shortening ED LOS is not clear. The effects of implementation of more sensitive EMS tools to screen patients with suspected AMI and analyses of the effects of these tools on the ED care process are needed. Considering that over half of AMIs were not recognized at the prehospital level, the creation and use of advanced patient-assessment protocols at the scene could have clinical benefits.

This study had several limitations. First, prehospital recognition was dependent on individual experience or competency. There was no standardized EMS protocol to evaluate patients with suspected AMI based on the patient's history, which is a significant limitation. Second, we could not confirm whether prehospital information was actually delivered to ED physicians. Although ED triage nurses write a triage note containing information provided by EMS personnel, it is entirely up to the physician as to whether they refer to this note or not. Next, information on the time of diagnosis, time to first 12-lead ECG at the ED, or time to consult cardiologist would provide more accurate information on the effect of prehospital recognition, but this information was not available in the databases. As ED LOS is a surrogate marker, we adjusted for factors affecting the ED LOS as much as possible. However, there were also unadjusted confounders such as administrative delays and preparation time in the ward or ICU. We included time and season of ED visit in the main analysis to adjust for variation, but variation remains a significant limitation of the study. However, when further sensitivity analysis excluding extremely delayed cases (10, 12, and 15 hours) was conducted, we observed the same trends (Supplementary Table 1). Fourth, even though chief complaints and vital signs were adjusted for, detailed condition severity or characteristics were not analyzed. Generally, the ED LOS of patients with minor AMI or late presenters is prolonged due to ambiguous histories. Furthermore, we could not evaluate this association in the STEMI cohort as the majority of these patients stayed in the ED for less than 4 hours. We hypothesized that shortening of ED LOS would affect the treatment outcomes of AMI, which would shorten IP LOS and increase survival. There was no significant association between prehospital recognition and IP LOS and survival, suggesting that a delay in the ED might be tolerated in non-severe patients. Fifth, individual variations in practice could affect the results, such as physicians who always check for cardiovascular disease, cardiologists who respond quickly, and physicians who tend to skip performing laboratory tests in patients without certain needs. Compliance with hospitalization may also have affected our findings. Since the design of this study was observational, unmeasured biases may have been present. Last, the results of this study cannot be generalized because this study was conducted using data from three academic tertiary emergency departments and a basic-to-intermediate service level EMS system.

In summary, prehospital recognition of AMI by EMS personnel was found to be associated with a short ED LOS in EMS-transported AMI patients. Focused assessment at the scene can improve the clinical outcomes of AMI patients by decreasing their ED LOS.

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Multivariable logistic regression by prehospital recognition with or without 12-lead electrocardiography excluding the extremely delayed cases

Supplementary material is available at https://doi.org/10.15441/ceem.22.330.

CONFLICT OF INTEREST

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

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AUTHOR CONTRIBUTIONS

Conceptualization: SRS, KHK; Data curation: KJS, SDS; Formal analysis: SRS, KHK; Investigation: SRS, KHK; Methodology: JHP, KHK; Project administration: KJS, SDS; Resources: KJS, SDS; Soft-

ware: SRS, KHK; Supervision: JHP; Validation: JHP; Visualization: SRS, KHK; Writing–original draft: SRS, KHK; Writing–review & editing: all authors.
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Supplementary Table 1. Multivariable logistic regression by prehospital recognition with or without 12-lead electrocardiography excluding the extremely delayed cases

Outcome	Adjusted odds ratio (95% confidence interval)		
	≤ 15 Hr	≤ 12 Hr	≤ 10 Hr
ED LOS < 4 hr			
Group A	1.00	1.00	1.00
Group B	1.57 (1.14–2.16)	1.51 (1.09–2.10)	1.61 (1.14–2.27)
Group C	1.70 (1.16–2.49)	1.74 (1.19–2.59)	1.85 (1.22–2.79)
Inpatient LOS < 4 day			
Group A	1.00	1.00	1.00
Group B	1.02 (0.75–1.39)	1.05 (0.77–1.45)	1.06 (0.76–1.46)
Group C	1.20 (0.83–1.74)	1.21 (0.83–1.77)	1.33 (0.91–1.96)
Survival to discharge			
Group A	1.00	1.00	1.00
Group B	0.99 (0.52–1.89)	0.89 (0.46–1.74)	0.86 (0.44–1.68)
Group C	1.23 (0.54–2.80)	1.23 (0.51–2.98)	1.23 (0.51–2.99)

The multivariable model was adjusted for age group, sex, past heart disease history, chief complaint, prehospital shock, prehospital alertness, time of visit, weekend, and season.
ED, emergency department; LOS, length of stay.

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Original Article

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Head computed tomography for elderly patients with acute altered mental status in the emergency setting: value for decision-making and predictors of abnormal findings

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Objective This study evaluated the impact of head computed tomography (CT) on clinical decision-making about older adults with acute altered mental status (AMS) in the emergency department in terms of CT's diagnostic yield, emergency department length of stay, and changes in medical strategy. It also attempted to find predictors of an acute imaging abnormality.

Methods This was a 1-year, retrospective, single-center observational study of patients aged ≥75 years who underwent noncontrast head CT because of an isolated episode of AMS. The acute positive CT findings were ischemic strokes, hemorrhages, tumors, demyelinating lesions, hydrocephalus, and intracranial infections.

Results A total of 594 CTs were performed, of which 38 (6.4%) were positive. The main etiology of AMS was sepsis (29.1%). Changes in medical strategy were more common in patients with a positive CT, and the major changes were ordering additional neuro exams (odds ratio [OR], 95.3; 95% confidence interval [CI], 38.4–233.8; P<0.001), adjusting treatments (OR, 12.2; 95% CI, 5.0–29.5; P<0.001), and referral to a neurologic unit (OR, 7.3; 95% CI, 3.0–17.5; P<0.01). Three factors were significantly associated with a positive outcome: Glasgow Coma Scale <13 (OR, 8.5; 95% CI, 2.3–28.9; P<0.001), head wound (OR, 3.1; 95% CI, 1.1–8.2; P=0.025), and dehydration (OR, 0.3; 95% CI, 0.1–0.4; P=0.021). For elderly patients with a Glasgow Coma Scale ≥13 and no head wound or clinical dehydration, the probability of a positive CT was 0.02 (95% CI, 0.01–0.04). Considering only those patients, the diagnostic yield fell to 1.7%.

Conclusion In elderly patients, the causes of AMS are primarily extracerebral. Randomized clinical trials are needed to validate a clinical pathway for selecting patients who require emergent neuroimaging.

Keywords Emergency medicine; Confusion; Sprial computed tomography; Diagnostic imaging; Resource allocation

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Capsule Summary

What is already known

Previous studies have evaluated the relevance of emergent head computed tomography (CT) in nonselected cohorts. They recommended that neuroimaging be ordered for confused patients with new focal neurological signs or suspected traumatic brain injury without an age criterion. However, when treating the increasing number of elderly patients in emergency departments, isolated acute mental status changes are still a challenging reason for using emergent head CT.

What is new in the current study

In an elderly population, the diagnostic yield of head CT for isolated altered mental status was very low. Although ordering a head CT significantly affected the emergency department length of stay, changes in the initial medical strategy based on the CT scan results were rare. CT scans could be deemed unnecessary, in patients with a Glasgow Coma Scale ≥ 13, the absence of a head wound, and the presence of clinical dehydration.

INTRODUCTION

Acute altered mental status (AMS) is a common presentation for elderly people in an emergency department (ED) and describes "any changes in a patient's baseline status," including "variable time courses and degrees of severity" such as confusion, altered behavior, disorientation, alertness, delirium, or coma.[1,2] AMS accounts for 4% to 10% of all ED admissions[1,3,4] and approximately 40% of ED admissions among elderly patients.[4-7] AMS should be considered as an acute brain failure that highlights the brain's vulnerability and decreased cognitive reserve precipitated by an underlying medical illness.[8] It increases both the long-term risk of dementia and 1-year mortality.[9-11] Because EDs are the leading hospital point of entry for an increasing number of elderly patients, emergency physicians (EPs) should be able to identify triggering factors and initiate early treatments adapted to many underlying conditions. The etiologies of AMS are mainly extracerebral, including infections, hydroelectrolytic disorders, and medications.[3,8,12] However, ED neuroimaging is increasingly used[13-15] to evaluate confused elderly patients, as often as in 14% to 21% of cases.[16] Some researchers have expressed concern about how that increase in neuroimaging is improving patient outcomes.[14,17] For EPs, the challenge is to quickly differentiate confused elderly patients who need an emergent head computed tomography (CT) scan from those who have an extracerebral cause of AMS.

Our aim in this study was to determine how emergent head CT in elderly patients with isolated, acute AMS affected EP decision-making in terms of three critical criteria: diagnostic yield, ED length of stay related to CT use, and changes in the initial medical strategy. We also sought predictors of acute cerebral lesions for which imaging could be useful.

METHODS

Ethical statements

This study was approved by the Institutional Ethics Committee of the Hospital Paris Saint-Joseph (No. IRB00012157) and registered at ClinicalTrials.gov (No. NCT 04929704). French research regulation states that written consent from the patients is not mandatory, but investigators are required to give each patient an informational leaflet explaining the purpose of the research. Those informational documents were addressed to all eligible patients (Official Journal of the French Republic, 0160; July 13, 2018; paragraph 110, MR-004). For patients with legal protection, the informational documents were addressed to the patient's legal guardian (guardianship or curatorship). After a period of 1 month, if the patient or guardian had not contacted the investigator, it was established that the patient did not oppose the use of his or her data. The patients' information and nonopposition to the use of their data for research was also collected in accordance with European regulations (General Data Protection Regulation). All data were extracted from our computerized medical record system (Dx-Care ver. 12.2.0.1.0; Medasys, Le Plessis-Robinson, France). The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents. The authors vouch for the accuracy and completeness of the data and analyses and for the fidelity of the study to the protocol.

Design and settings

This was an investigator-initiated, retrospective, and observational cohort study evaluating the effects of head CT and the predictors of acute anomalies in elderly patients presenting with isolated AMS at their admission to a single ED. The cohort included patients seen from January 1, 2019 to December 31, 2019 in the

ED of Hospital Paris Saint-Joseph, in Paris, France, a tertiary urban hospital with approximately 700 beds and 59,350 annual ED encounters. Data from 2020 were not used because of potential bias related to the COVID-19 pandemic.

Cohort definition

The cohort was drawn from consecutive patients aged ≥ 75 years who underwent a noncontrast helical head CT scan in the ED. That age criterion was chosen because it is the age requirement for geriatric units in France.[18] Head CT scans were performed on a Revolution Frontier CT scanner (GE Healthcare, Chicago, IL, USA) with a total dose length product of 755.44 mGy.cm, a volume CT dose index of 45.09 mGy, a slice thickness of 0.6 mm, and a pitch value of 0.5. The decision to perform a CT was made by the attending EP. The suspected disease to confirm or rule-out using CT was evaluated retrospectively by two independent EPs who examined each medical record and the CT referral forms. The interpretation of the CTs was done by a senior radiologist through an official written report, in accordance with the current practice in our hospital. The inclusion criteria for this study were the presence of an acute AMS, defined as new onset behavioral and cognitive change associated with a Glasgow Coma Scale (GCS) < 15 with or without disorientation, loss of memory, altered consciousness, hallucination, agitation, or persecution delirium within the past 1 month. The AMS analysis considered only the past month because it has already been shown that patients who have AMS for more than 1 month very rarely have potentially treatable intracranial lesions.[19] Also, AMS for more than 1 month is included in the diagnostic framework for dementia.[3] Patients with an unequivocal reason to order neuroimaging were excluded: concomitant localizing neurological signs (abnormalities of the cranial nerves, meningeal syndrome, cerebellar syndrome, aphasia, vestibular syndrome, sensory, or motor deficit); head trauma on anticoagulant or antiplatelet treatment; major head trauma, such as a traffic accident, except falls from height; unusual headache; and coma, defined as GCS ≤ 8. A patient who visited the ED with nonrelated episodes of AMS could be included more than once in this study.

Variables and outcomes

The primary endpoint was the rate of positive head CTs in the cohort, defined as an imaged finding of a recent intracranial lesion that explained the AMS. The following conditions were considered positive findings: acute ischemic strokes, acute hemorrhages, recent cerebral tumors, recent demyelinating lesions, acute hydrocephalus, and intracranial infections. Imaging lesions of primary dementia (cerebral atrophy, leukoaraiosis, periventricular lesions, arterial calcifications, microbleeds, or dilatation of Virchow-Robin spaces) or secondary dementia (chronic hydrocephalus, meningioma or hygroma, neurosurgery stigmas, or chronic vascular lesions) were classified as negative findings even if they were a predisposing condition for AMS. All other abnormalities were considered to be negative findings.

The secondary endpoints were the following. First, the rate of 48-hour changes in medical strategy based on the head CT outcomes (positive or negative). The following were considered to be changes in medical strategy: changes in diagnostic approach (use of additional neuro exams, such as brain magnetic resonance imaging [MRI], electroencephalogram, head CT monitoring, or an incidental finding that changed the care approach), changes in the therapeutic approach (withdrawal or initiation of antiplatelet, anticoagulant, or antiepileptic agents or endovascular or neurosurgical treatments), and changes in referral decisions (admission to a stroke unit or the neurology or neurosurgery department). Second, the ED length of stay related to head CT use (i.e., time between head CT order and interpretation by a senior radiologist through a written official report). Lastly, the factors (historical, clinical, and biological) that predict a positive head CT. Clinical dehydration was defined using tachycardia (> 100 beats/min), low systolic blood pressure (< 100 mmHg), dry mucous membrane, dry axilla, poor skin turgor, sunken eyes, delayed capillary refill time (> 2 seconds), urine color, and saliva flow rate.[20]

Data collection

Key clinical features, radiological and biological parameters, and organizational data were collected retrospectively from computerized medical records. The primary endpoint was determined by the CT interpretation. Changes in the attending EP's medical strategy related to the CT result and the final etiology of AMS were assessed by two EPs.

Statistical analysis

This study followed the standards for reporting observational studies in the epidemiology guidelines. Continuous variables are reported as means with standard deviations or medians with interquartile ranges. The Shapiro-Wilk test was used to test the assumption of a normal distribution in each group. Student t-testing was used to compare normally distributed continuous variables, and the Wilcoxon test was used otherwise. Qualitative variables are reported as numbers with percentages and were compared with the chi-square test or Fisher exact test, as appropriate.

To determine the association between patient characteristics and the occurrence of the primary outcome, we first performed a

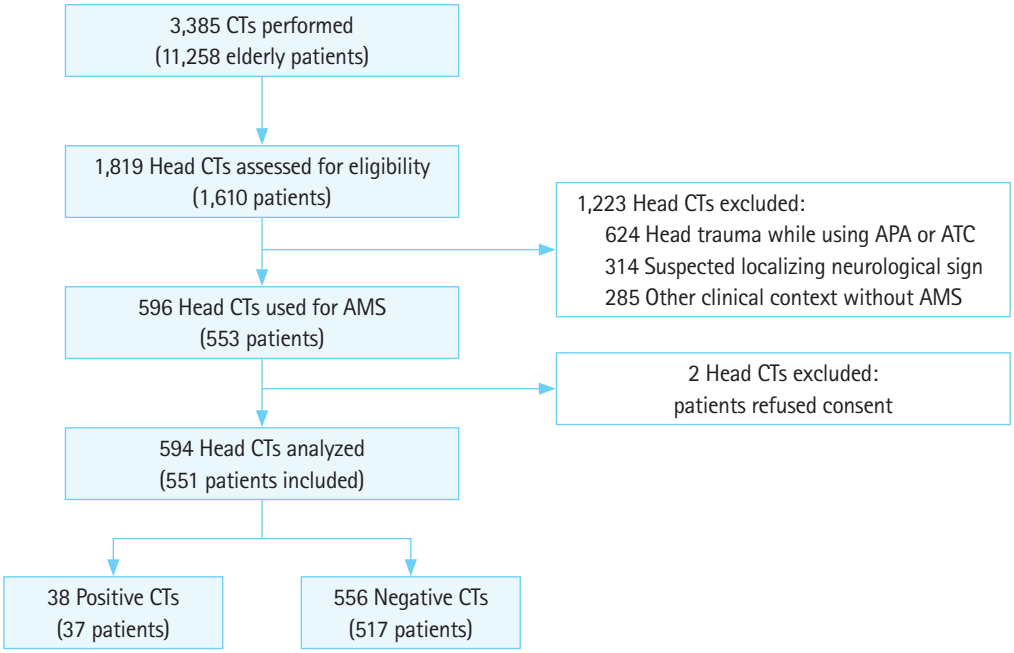

Fig. 1. Study flowchart. Head computed tomography (CT) performed per patient: one, 514 patients; two, 68 patients; and three, four patients. APA, antiplatelet agent; ATC, anticoagulant; AMS, altered mental status.

univariable analysis of all variables. Then, to adjust those associations for possible confounding factors, we tested a multivariable logistic model with all variables except those with insufficient data. The results are reported as odds ratios (ORs) with their 95% confidence intervals (CIs). The goodness of fit of the logistic regression analysis was ascertained using the Nagelkerke pseudo-R^2. Using that equation, we predicted the risk of having a positive CT. The CI of the prediction was obtained using its standard error, which we calculated as $\sqrt{(C' \times \text{covariance matrix} \times C)}$, where C is the linear combination of estimates, and C' is its transposition.

All statistical tests were two-tailed at the 0.05 level of significance. All data analysis was completed with R ver. 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Characteristics of the cohort

In 2019, 5.3 head CTs were performed per 100 elderly patients to search for an acute cerebral etiology for an isolated incident of AMS (Fig. 1). Those CTs affected 18.9% of elderly patients who visited the ED and accounted for 17.6% of all CTs and 32.7% of head CTs ordered for elderly patients. This corresponded to a total of 596 head CTs for 553 patients. Two of those patients refused to consent to this study. Of the 594 CTs analyzed, the mean patient age was 87.3 ± 6.4 years, and the 1-year mortality rate was 8.4%. Among the study population, 249 patients (41.9%) had dementia, 83 (13.9%) had a history of stroke, and 38 (6.4%) had ever had a brain hemorrhage. The medical history of the enrolled patients is summarized in Table 1. The key clinical features and diagnostic work-ups of the attending EPs are reported in Table 2.

Main results

Of the 594 head CT scans completed, 38 found a lesion that explained the symptoms, for a diagnostic yield of 6.4% (Table 1). The main cerebral etiology was acute brain hemorrhage (60.5%), including 16 cerebral or subarachnoid hemorrhages (42.1%), and seven acute-on-chronic subdural hematomas (18.4%), i.e., visualization of extra-axial fluid layers of varying densities separated by internal membranes (Table 3). Of the 38 positive head CTs, 29 (76.3%) led to changes in the prescan management plan, mainly in the form of orders for additional neuro exams (65.8%) rather than by adjusting treatments (42.1%) or referrals to a neurological unit (34.2%). Eleven patients underwent an additional MRI within the first 48 hours (six after a positive CT and five after a negative CT) (Table 3). Two acute ischemic strokes that involved the temporal area were diagnosed on the additional MRI despite a normal CT result (Table 4). Imaging showed significantly more predisposing conditions of AMS, i.e., anomalies of primary dementia, in patients with a negative head CT than a positive head CT (44.7% vs. 77.9%), with an OR of 0.23 (95% CI, 0.12–0.45; $P < 0.001$) (Table 3). The rates of anomalies indicating secondary dementia were similar regardless of the outcome (29.0% vs. 34.0%,

Table 1. Baseline characteristics of the cohort according to the head CT outcome

Characteristic	Overall (n = 594)	Positive CT (n = 38)	Negative CT (n = 556)	OR (95% CI)	P-value
Age (yr)	87.3 ± 6.4	86.9 ± 5.9	87.2 ± 6.5	-	0.767
Male sex	380 (64.0)	19 (50.0)	361 (64.9)	1.85 (0.96–3.58)	0.064
Underlying condition					
Dementia[a]	249 (41.9)	14 (36.8)	235 (42.3)	0.80 (0.40–1.57)	0.512
Psychiatric disorder	96 (16.2)	6 (15.8)	90 (16.2)	0.97 (0.39–2.39)	0.949
Parkinson	37 (6.2)	1 (2.6)	36 (6.5)	0.39 (0.05–2.93)	0.501
Epilepsia	39 (6.6)	1 (2.6)	38 (6.8)	0.37 (0.05–2.76)	0.501
Ischemic stroke or TIA history	83 (14.0)	2 (5.3)	81 (14.6)	0.33 (0.08–1.38)	0.109
Brain hemorrhage history	38 (6.4)	2 (5.3)	36 (6.5)	0.80 (0.19–3.47)	> 0.999
Cancer history	68 (11.4)	4 (10.5)	64 (11.5)	0.90 (0.31–2.63)	> 0.999
Chronic kidney disease[b]	51 (8.6)	5 (13.2)	46 (8.3)	1.67 (0.62–4.49)	0.362
Medication[c]					
Anticoagulant	111 (20.6)	3 (7.9)	108 (19.4)	0.36 (0.11–1.18)	0.078
Antiplatelet	137 (25.4)	7 (18.4)	130 (23.4)	0.74 (0.32–1.72)	0.483
Benzodiazepine	138 (25.6)	7 (18.4)	131 (23.6)	0.71 (0.30–1.67)	0.436
Neuroleptic	49 (9.1)	0 (0)	49 (8.8)	-	0.062
Opioid	16 (3.0)	2 (5.7)	14 (2.5)	2.13 (0.46–9.75)	0.278
Anticholinergic	179 (33.1)	7 (18.4)	172 (30.9)	0.48 (0.21–1.13)	0.088
Diuretic	92 (17.0)	4 (11.4)	88 (15.8)	0.61 (0.21–1.78)	0.361
Context					
Fall	294 (49.5)	25 (65.8)	269 (48.4)	2.05 (1.03–4.09)	0.038
Head trauma	121 (20.4)	14 (36.8)	107 (19.2)	2.45 (1.23–4.89)	0.009
Infection < 1 mo	67 (11.3)	3 (7.9)	64 (11.5)	0.66 (0.20–2.20)	0.789
Alcohol use	8 (1.3)	0 (0)	8 (1.4)	-	> 0.999
Epileptic seizure	12 (2.0)	1 (2.6)	11 (2.0)	1.34 (0.17–0.65)	0.551
Outcome					
Hospitalization	486 (81.8)	35 (92.1)	451 (81.1)	2.72 (0.82–9.00)	0.089
Death in the year	50 (8.4)	4 (10.5)	46 (8.3)	1.30 (0.44–3.84)	0.550

Values are presented as mean±standard deviation or number (%). No OR for continuous variables and neuroleptic treatment (headcount, 0).
CT, computed tomography; OR, odds ratio; CI, confidence interval; TIA, transient ischemic attack.
[a]Alzheimer, Lewy, and Korsakoff diseases, normal pressure hydrocephalus, vascular dementia, and unspecified dementia. [b]592 Overall (37 positive CT and 555 negative CT). [c]540 Overall (35 positive CT and 505 negative CT).

P = 0.524), except for the rate of chronic hematoma, which was higher in the positive CT group than in the negative CT group (13.2% vs. 1.6%), with an OR of 9.21 (95% CI, 2.92–29.03; P < 0.001) (Table 3). Among the 23 patients with hemorrhages, one patient was included twice for incidents of AMS within the previous 24 hours after head traumas with wounds. His two CTs, taken 8 weeks apart showed, acute-on-chronic subdural hematomas.

Among the 556 negative CTs, the main cause of AMS was sepsis (29.1%), especially from urinary tract infections (15.3%), followed by dementia with no other associated etiology (21.6%) (Table 4). Overall, there was no statistical difference between the median times needed to request, perform, and interpret CT scans, regardless of the outcome (P-values of 0.626, 0.865, and 0.818, respectively). The median time for CT interpretation was 104 minutes and accounted for 22.0% of the ED length of stay, regardless of the outcome (P = 0.614) (Table 3). In an additional query of our database of elderly ED patients during the study period, we found that our cohort's ED length of stay was higher than that of the 3,385 older patients who received any type of CT (median, 560 minutes vs. 372 minutes) and higher than that of the 7,873 who did not receive a CT (median, 560 minutes vs. 210 minutes) (Table 3 and Fig. 1).

Prediction of a positive CT scan

Table 5 shows the results of the logistic regression analysis of demographic, clinical, and biological parameters that could predict a positive CT result. Two variables were significantly predictive of a positive CT finding: a GCS < 13, with an OR of 8.50 (95% CI, 2.30–28.87; P < 0.001), and a head wound, with an OR of 3.06 (95% CI, 1.14–8.21; P = 0.025). One variable tended to exclude a positive CT finding: clinical dehydration, with an OR of 0.29 (95% CI, 0.09–0.77; P = 0.021).

Fig. 2 shows the predictive values of the three clinical presen-

Table 2. Emergency physician diagnostic work-up of altered mental status according to the head CT outcome

Variable	Overall (n = 594)	Positive CT (n = 38)	Negative CT (n = 556)	OR (95% CI)	P-value
Vital sign					
GCS (9–15)	14.2 ± 0.8	13.7 ± 1.0	14.2 ± 0.8	-	< 0.001
GCS ≥13	573 (96.5)	33 (86.8)	540 (97.1)	0.20 (0.07–0.57)	0.008
Heart rate (beats/min)	81.6 ± 18.2	77.8 ± 14.7	81.8 ± 18.4	-	0.184
Systolic blood pressure (mmHg)	141.9 ± 25.7	138.4 ± 24.1	142.1 ± 25.8	-	0.388
Body temperature (°C)	36.8 ± 0.6	36.8 ± 0.4	36.8 ± 0.6	-	0.851
Altered mental status					
Onset (day)					0.966
< 1	303 (51.1)	20 (52.6)	283 (50.9)	1.00	
1–7	87 (14.6)	5 (13.2)	82 (14.7)	0.87 (0.32–2.40)	
> 7	204 (34.3)	13 (34.2)	191 (34.4)	0.96 (0.47–1.98)	
Hallucination or agitation or delirium	144 (24.2)	7 (18.4)	137 (24.6)	0.69 (0.30–1.60)	0.387
Acute disorientation	512 (86.2)	31 (81.6)	481 (86.5)	0.69 (0.29–1.62)	0.394
Acute loss of memory	463 (77.9)	25 (65.8)	438 (78.8)	0.52 (0.26–1.04)	0.062
Alertness	311 (52.4)	17 (44.7)	294 (52.9)	0.72 (0.37–1.40)	0.331
Clinical feature					
Head wound	93 (15.7)	14 (36.8)	79 (14.2)	3.52 (1.75–7.10)	< 0.001
Dehydration[a]	204 (34.3)	5 (13.2)	199 (35.8)	0.27 (0.10–0.71)	0.005
Oxygen requirement	95 (16.0)	3 (7.9)	92 (16.5)	0.43 (0.13–1.44)	0.159
Urinary retention	60 (10.1)	2 (5.3)	58 (10.4)	0.48 (0.11–2.03)	0.412
Rectal exam performed	183 (30.8)	8 (21.1)	175 (31.5)	0.58 (0.26–1.29)	0.178
Fecaloma	43 (7.2)	1 (2.6)	42 (7.6)	0.33 (0.04–2.47)	0.511
Infectious trigger	228 (38.4)	4 (10.5)	224 (40.3)	0.17 (0.06–0.50)	< 0.001
Additional exam					
Electrocardiogram	373 (62.8)	25 (65.8)	348 (62.6)	1.15 (0.58–2.30)	0.693
Chest X-ray	318 (53.5)	15 (39.5)	303 (54.5)	0.54 (0.28–1.07)	0.072
Urine dipstick	360 (60.6)	20 (52.6)	340 (61.2)	0.71 (0.37–1.36)	0.298
Cytobacterial urinary	229 (38.6)	12 (31.6)	217 (39.0)	0.72 (0.36–1.46)	0.361
Biological parameter				-	
Glucose (mmol/L)	6.9 ± 3.1	7.6 ± 5.5	6.9 ± 2.9		0.611
Sodium (mmol/L)[b]	139.9 ± 5.3	140.53 ± 4.1	139.82 ± 5.4		0.409
Calcium (mmol/L)[c]	2.4 ± 0.1	2.4 ± 0.1	2.4 ± 0.2		0.628
Creatinine (μmol/L)[b]	81.0 (63.0–110.0)	81.5 (70.5–105.7)	80.0 (62.0–110.0)		0.407
Proteins (g/L)[d]	71.0 ± 6.3	70.6 ± 4.5	71.1 ± 6.4		0.987
C-reactive protein (mg/L)	24.5 (8.6–59.7)	18.8 (7.3–47.6)	24.6 (8.8–59.9)		0.443

Values are presented as mean ± standard deviation, number (%), or median (interquartile range). No OR for continuous variables.
CT, computed tomography; OR, odds ratio; CI, confidence interval; GCS, Glasgow Coma Scale.
[a]Clinical dehydration was diagnosed using tachycardia (> 100 beats/min), low systolic blood pressure (< 100 mmHg), dry mucous membrane, dry axilla, poor skin turgor, sunken eyes, delayed capillary refill time (> 2 seconds), urine color, and saliva flow rate. [b]592 Overall (38 positive CT and 554 negative CT). [c]270 Overall (15 positive CT and 255 negative CT). [d]592 Overall (38 positive CT and 554 negative CT).

tations associated with a positive CT finding, both alone and together. In the absence of any risk factor (GCS ≥ 13, no head wound, and presence of clinical dehydration), the probability of a positive CT finding was 2.0%. Thus, three of the 181 concerned patients (1.7%) had a positive CT finding: two had acute hydrocephalus that did not require a change in their medical strategy, and one had a cerebral tumor and was referred to neurosurgery. By contrast, in the presence of a GCS < 13, a head wound, and no dehydration, the risk of a positive CT finding was 32.0%. Thus, five of the 13 concerned patients (38.4%) had a positive CT finding: two subarachnoid hemorrhages, one ischemic stroke (temporal area), one acute-on-chronic subdural hematoma, and one discovery of a cerebral tumor. One of those patients died during the 1-year follow-up. For patients with a GCS ≥ 13 and no head wound who were not clinically dehydrated, the risk of a positive CT finding was 4.6%. Thus, of the 481 patients concerned, 20 had a positive CT: five acute hydrocephalus, four acute-on-chronic subdural hematomas, four brain hemorrhages (i.e., parenchymal or subarachnoid), four tumors, and three ischemic strokes. Those findings led to a change in the initial medical strategy for 15 pa-

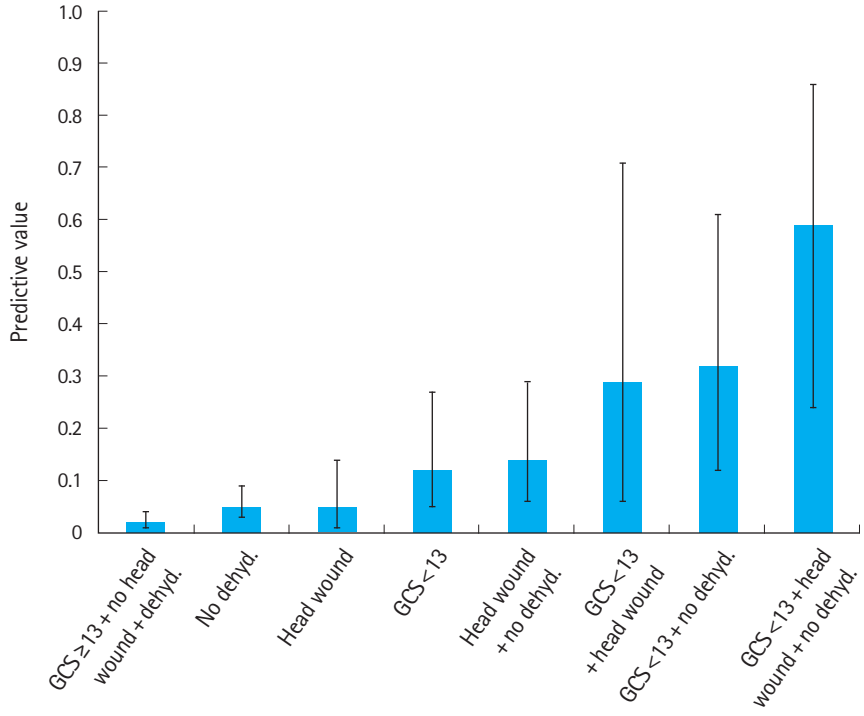

Fig. 2. Predictive values of clinical variables for a positive head computed tomography. Error bars indicate 95% confidence interval. GCS, Glasgow Coma Scale; dehyd., dehydration.

tients, mainly the prescription of additional neruo exams (n = 12) or treatment adjustments (n = 10), rather than referrals to specialists (n = 8).

Of the 556 patients with negative CT results, five underwent an additional MRI during their hospitalization (Table 3). All of them had a GCS of 14 and CT findings of secondary dementia with vascular lesions (i.e., old infarcts). Among them, two patients who had a GCS of 14, no head wound, and were not clinically dehydrated were diagnosed with a temporal ischemic stroke on an additional brain MRI (Table 4). One patient had a head wound with no dehydration and a normal brain MRI. One patient was clinically dehydrated, had a GCS of 14, and no head wound and had a normal brain MRI.

DISCUSSION

Given the increasing number of elderly patients being seen in EDs, deciding whether an emergent head CT is indicated for acute AMS is a growing diagnostic challenge.[14,16] Despite current guidelines,[21,22] a third of 1,819 head CTs were ordered to investigate a potential cerebral etiology for an isolated AMS, and positive findings were rare (6.4%) in a busy, urban ED. Our findings are consistent with a previous retrospective study showing that delirium or disorders of consciousness were among the main reasons for requesting head CTs in a similar emergency setting (21.0% and 14.0%, respectively).[16] This concern for misdiagnosing a cerebral lesion can be explained by common, vaguely related histories in confused patients.[23] The large number of diagnostic resources used per patient and overall long ED stays clearly reflect the diagnostic complexity of this clinical setting. Almost all patients had a blood exam, and more than 50% underwent an electrocardiogram, a urine dipstick, and a chest X-ray, as recommended in the guidelines.[22] Most of these elderly patients (82%) were hospitalized after their ED visit, regardless of their head CT scan results (P = 0.09).

One multicenter Chinese study in a younger ED cohort stated that CT use might not delay patient outcomes.[24] However, we found that the ED length of stay was higher in this cohort (560 minutes) than in the overall ED population of patients aged ≥ 75 years, both for those who had another type of CT and those who did not have CT (372 and 210 minutes, respectively). When the overall time between the order for a CT scan and its interpretation affects the time spent in the ED by 22.0%, we cannot ignore the association between the ED length of stay and the occurrence of adverse events among elderly patients, as demonstrated by Considine et al.[25] Furthermore, an ED admission and long length of stay are themselves precipitating factors of AMS, with attendant complications of wandering and falls, agitation, chemical

Table 3. Primary and secondary outcomes

Head CT outcome	Overall (n = 594)	Positive CT (n = 38)	Negative CT (n = 556)	OR (95% CI)	P-value
Positive finding			-		
Acute hemorrhages[a]	16 (2.7)	16 (42.1)			
Acute-on-chronic subdural hematomas	7 (1.2)	7 (18.4)			
Brain tumor	6 (1.0)	6 (15.8)			
Acute hydrocephalus	5 (0.8)	5 (13.2)			
Acute ischemic strokes	4 (0.7)	4 (10.5)			
Chronic anomaly					
Lesions of primary dementia[b]	450 (75.8)	17 (44.7)	433 (77.9)	0.23 (0.12–0.45)	< 0.001
Lesions of secondary dementia	200 (33.7)	11 (28.9)	189 (34.0)	0.79 (0.38–1.63)	0.524
Vascular lesions[c]	116 (19.5)	5 (13.2)	111 (20.0)	0.61 (0.23–1.59)	0.306
Chronic subdural hematoma	14 (2.4)	5 (13.2)	9 (1.6)	9.21 (2.92–29.03)	< 0.001
Meningioma or hygroma	17 (2.9)	0 (0)	17 (3.1)	-	0.617
Chronic hydrocephalus	10 (1.7)	2 (5.3)	8 (1.4)	3.81 (0.78–18.58)	0.130
Neurosurgery stigmas	8 (1.3)	0 (0)	8 (1.4)	-	0.457
48-Hour change	51 (8.6)	29 (76.3)	22 (4.0)	78.21 (33.07–184.99)	< 0.001
Diagnostic management[d]	36 (6.1)	25 (65.8)	11 (2.0)	95.28 (38.84–233.75)	< 0.001
Therapeutic adjustment[e]	27 (4.5)	16 (42.1)	11 (2.0)	12.17 (5.02–29.50)	< 0.001
Referral decision[f]	26 (4.4)	13 (34.2)	13 (2.3)	7.28 (3.03–17.47)	< 0.001
Operational influence				-	
Head CT order[g] (min)	85.5 (45.3–158.0)	86.0 (46.0–158.3)	76.5 (43.5–137.0)		0.626
Head CT performance[h] (min)	54.5 (26.0–106.0)	53.0 (26.0–107.8)	61.5 (28.3–96.3)		0.865
Head CT interpretation[i] (min)	104.0 (70.0–172.3)	102.5 (68.0–172.8)	104.5 (70.0–170.8)		0.818
ED length of stay[j] (min)	560.5 ± 260.5	598.4 ± 236.2	557.9 ± 262.1		0.355
Head CT interpretation/ED length of stay	0.2 (0.14–0.34)	0.2 (0.14–0.34)	0.2 (0.14–0.34)		0.614

Values are presented as the number (%), median (interquartile range), or mean ± standard deviation. No OR for continuous variables.
CT, computed tomography; OR, odds ratio; CI, confidence interval; ED, emergency department.
[a]Parenchymal or subarachnoid. [b]Cerebral atrophy, leukoaraiosis, periventricular lesions, arterial calcifications, microbleeds, or dilatation of Virchow-Robin spaces. [c]Chronic ischemia and lacunar infarctions. [d]Additional neurological exams: 11 brain magnetic resonance imaging (six after positive CTs and five after negative CTs), five electroencephalograms, 16 second CTs. [e]Withdrawal or initiation of antiplatelet, anticoagulant, or antiepileptic agents or endovascular or neurosurgical treatments. [f]Hospitalization in stroke unit or neurology or neurosurgery departments. [g]From the first medical evaluation to the order of CT. [h]From the order to the CT performance. [i]From the order to the interpretation via written report by the radiologist. [j]ED length of stay in the overall population of patients aged ≥ 75 years during the study period: 3,385 any type of CT, 210 minutes (range, 336–466 minutes); 7,873 no CT, 372 minutes (range, 479–625 minutes).

and mechanical restraint, inappropriate use of benzodiazepines and neuroleptics, and increased time spent in a noisy and stressful environment.[26] Whether or not head CT helps in the management of patients in the ED remains controversial in patients with no focal neurological signs and no major head injury.[17] In this clinical setting, our results also address whether ordering emergency neuroimaging in elderly patients with AMS alone leads to effective diagnostic, therapeutic, or referral intervention.

With the increasing use of CT imaging in EDs, our analysis suggests a scope for future intervention studies to evaluate the accuracy of clinical prediction rules for identifying intracranial lesions in elderly patient with isolated AMS. Previously, the utility of head CT for evaluating AMS in emergency medicine has mainly been studied through reviews of nonselected cohorts, including patients who have a high risk of cerebral lesions because of neurological signs,[27-32] traumatic brain injuries,[33,34] unusual headaches,[35] or the use of antiplatelet or anticoagulant treatments.[32,36] Few studies have specifically examined elderly patients undergoing head CT in EDs for isolated AMS, but that situation accounted for 14% to 30% of head CT requests.[16,37] Comparison with other emergency settings is limited by the inclusion of younger patients (means ranging from 66 to 73 years vs. 87 years in our cohort)[27,31] and the presence of focal neurological signs (33% to 60%),[16,27,31] which was an exclusion criterion for our analysis. The diagnostic yields in those previous studies were higher than those in our selected population by 10% to 40%.[27,31,38] Our low diagnostic yield also differs from that of a retrospective study of 170 patients referred to a geriatric unit for confusion.[19] That previous study considered confusion, decreased alertness, and seizure, and its diagnostic yield was higher than in our setting: about 18.0% of their 68 patients had an intracranial cause of confusion.[19] That difference might be explained by the high prevalence of cerebral tumors (16%) related to the inclusion of patients with confusion lasting for less than 1 year.[19] Most of all, it probably reflects the

Table 4. Main etiology of altered mental status in patients with a negative head computed tomography

Etiology	Negative CT (n = 556)
Sepsis	162 (29.1)
Urinary tract infection	84 (15.1)
Respiratory tract infection	48 (8.6)
Other infections[a]	29 (5.2)
Dementia	120 (21.6)
Central nervous system disease	66 (11.9)
Postconcussion syndrome	35 (6.3)
Postictal confusion	22 (4.0)
Transient global amnesia	5 (0.9)
Other central diseases[b]	5 (0.9)
Rhabdomyolysis	64 (11.5)
Metabolic encephalopathies	39 (7.0)
Sodium disorder	31 (5.6)
Hypoglycemia	4 (0.7)
Uremic encephalopathy	3 (0.5)
Hepatic encephalopathy	1 (0.2)
Urinary retention and/or fecaloma	33 (5.9)
Cardiac disorder	29 (5.2)
Medication	18 (3.2)
Psychiatric disorder	12 (2.2)
Acute alcohol intoxication	7 (1.3)
Joint pain	5 (0.9)
Undetermined	1 (0.2)

[a]Sixteen cutaneous, nine gastrointestinal, four articular. [b]One previous cerebral tumor, two acute ischemic strokes involving the temporal area (diagnosed on mangnetic resonance imaging during hospitalization), one meningitis, and one migraine.

Table 5. Multivariable analysis of factors predictive of positive head computed tomography

Variable	OR (95% CI)	P-value[a]
Age	0.99 (0.93–1.05)	0.656
Male sex	1.65 (0.78–3.49)	0.190
Dementia, psychiatric disorder, or Parkinson	0.59 (0.28–1.22)	0.157
Anticoagulant or antiplatelet use	0.76 (0.30–1.86)	0.547
Fall	1.80 (0.72–4.46)	0.204
Head trauma	0.92 (0.31–2.79)	0.886
Infectious trigger	0.80 (0.17–2.75)	0.752
Glasgow Coma Scale < 13	8.50 (2.30–28.87)	< 0.001
Systolic blood pressure	0.99 (0.98–1.01)	0.227
Body temperature	0.90 (0.49–1.94)	0.775
Onset of AMS (day)		
> 7 vs. < 1	1.26 (0.38–3.60)	0.677
1–7 vs. < 1	1.56 (0.67–3.53)	0.292
Acute loss of memory	0.51 (0.24–1.13)	0.090
Glucose level	1.07 (0.97–1.16)	0.138
Sodium level	1.03 (0.96–1.09)	0.436
Creatinine level	1.00 (0.99–1.01)	0.953
Head wound	3.06 (1.14–8.21)	0.025
Dehydration	0.29 (0.09–0.77)	0.021

OR, odds ratio; CI, confidence interval; AMS, altered mental status.
[a]Nagelkerke pseudo-R^2 = 0.18.

increasing use of head CT during the 2000s without significant changes in imaging indications.[14,39] That suggests that other factors have become important explanations for the increased prescription of head CT for current geriatric patients.[14] Head CT is commonly available 24/7 in the radiology departments adjoining urban EDs.[15] Beyond operational factors, Broder and Warshauer[14] suggested that "the tolerance for diagnostic uncertainty" is falling among EPs, their consulting specialists (neurologists, geriatricians), and their patients. Presently, geriatric teams commonly want an extensive diagnostic work-up before they accept an admission.[14] A recent retrospective ED study over 4 years found a high diagnostic yield (9.8%) for head CT performed for AMS, but that rate decreased to 5.3% when considering a disorder of consciousness alone.[38]

A recent review of 294 ED patients recommended that neuroimaging be ordered for confused patients with new focal signs, suspected traumatic brain injury, suspected encephalitis, or no identifiable cause for delirium.[27] When their analysis was confined to 280 cases of acute isolated AMS, the diagnostic yield of CT was even lower (3%) than in our setting.[27] We suggest that that small difference occurred because complex structured examinations are often difficult in confused elderly patients. Indeed, some localized neurological signs might have been missed by the EPs. The main causes of isolated AMS in the previous study were the same as in our cohort: dementia (28%) in combination with medical or pharmacological conditions; medical conditions (11%) such as sepsis, dehydration, and metabolic disorders; dementia alone (8%); and multiple causes (8%).[27]

This study shows that ordering noncontrast head CTs for patients having an isolated AMS only when the three clinical variables are present at ED arrival could help to improve the diagnostic yield of cerebral lesions and prioritize appropriate medical strategies. A GCS < 13 is an important threshold for prioritizing patients who require a CT, with a high OR of 8.50 (95% CI, 2.30–28.87; P < 0.001).[16] This cutoff has been chosen to differentiate patients who present with only confused verbal responses (verbal score, 3 of 5) from those presenting with drowsiness that alters both the verbal score and the eye-opening score. It was also grounded on findings from a previous trial.[16] Although the GCS was originally designed to evaluate patients with a brain injury, it is now systematically recorded at ED admission for patients with acute brain injury or other conditions. It is easy to use and facilitates communication among emergency staff to detect neurological changes.[40]

In addition, we found that a history of minor head trauma,

falls, and antiplatelet or anticoagulant use did not individually result in positive CT findings among patients having only an acute AMS (ORs, 0.92, 1.80, and 0.76, respectively). On the other hand, the 3.06 OR value for a head wound is meaningful (95% CI, 1.14–8.21; P = 0.025) because it can be difficult for EPs to understand the timing, triggers, and effects of falling by elderly patients who appear to be only confused. This finding reinforces results from previous nonselected cohorts that recommended that emergent neuroimaging be reserved for patients suspected to have a brain injury or a fall.[16,27,32] It also confirmed a prior study showing that minor head traumas were not predictive of a positive CT.[35]

Based on the clinical variables available upon ED arrival, our results from a large emergency setting suggest a pathway that can avoid the use of unnecessary head CT in EDs and delay it until after initial diagnostic management in geriatric units or outpatient imaging centers. The very low adjusted OR of 0.29 (95% CI, 0.09–0.77; P = 0.021) for clinical dehydration combined with the predictive values of a GCS ≥13 and the absence of a head wound strongly suggest that emergent head CT not be used for those elderly patients. Of the 181 patients concerned (30.5%), only one CT result affected the initial medical strategy through the diagnosis of a cerebral tumor. This recommendation should not be applied to patients who are not clinically dehydrated because the risk of miss rate was about 5% (95% CI, 0.03–0.09). Our findings differ slightly from another ED study of 178 patients without an age criterion.[27] In that study, AMS without focal signs and with evidence for clinical dehydration or fever did not require neuroimaging.[27] In our cohort, neither the infectious context nor body temperature were predictive of a positive CT.

Our study has several limitations. First, it is a single-center study conducted in an urban ED with a high rate of elderly encounters (19%). This allowed us to provide a larger cohort of consecutive elderly patients than prior studies.[27,29-31,35,41,42] Second, our observations certainly require external validation because of our very low rate of positive CT findings, which makes the predictions of our model imprecise. Indeed, the quality of our data is not perfect, which is a limitation of any retrospective study, but we tried to limit potential bias by checking each head CT and medical record twice. Our analysis provides a reasonable cohort for a future randomized clinical trial to determine the actual effects of early ED imaging prioritization on medical management, ED length of stay, and miss rates. Third, we did not analyze elderly patients who presented with acute isolated AMS and did not receive head CT. They might have had an acute cerebral disease missed by the attending EP. That analysis would have required an additional review and follow-up of medical observations for all 11,258 elderly patients during the study period. In emergency settings with younger patients, prior studies reported that 40% to 60% of acute episodes of AMS were investigated through emergent neuroimaging (CT or MRI).[27,42] Because only a few patients received an additional MRI during follow-up, some small ischemic strokes might have been missed in patients with no etiology to explain their AMS except incipient dementia.

In summary, the yield of head CT in this elderly patient population remained lower than in the general population. In this retrospective cohort study, we have identified three clinical variables that can help improve resource allocation, limit unnecessary radiation exposure, and shorten the ED length of stay in the growing elderly population of emergency departments. These findings suggest that a prospective comparative study should be undertaken to design and validate specific clinical tools to limit the use of head CT in elderly patients at low risk of having a curable cerebral disease.

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: CG, MF, AF, GC; Formal analysis: CG, MF, AF, GC; Visualization: CG; Writing–original draft: all authors; Writing–review & editing: all authors.
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Development and validation of interpretable machine learning models for inpatient fall events and electronic medical record integration

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Objective Falls are one of the most frequently occurring adverse events among hospitalized patients. The Morse Fall Scale, which has been widely used for fall risk assessment, has the two limitations of low specificity and difficulty in practical implementation. The aim of this study was to develop and validate an interpretable machine learning model for prediction of falls to be integrated in an electronic medical record (EMR) system.

Methods This was a retrospective study involving a tertiary teaching hospital in Seoul, Korea. Based on the literature, 83 known predictors were grouped into seven categories. Interpretable fall event prediction models were developed using multiple machine learning models including gradient boosting and Shapley values.

Results Overall, 191,778 cases with 272 fall events (0.1%) were included in the analysis. With the validation cohort of 2020, the area under the receiver operating curve (AUROC) of the gradient boosting model was 0.817 (95% confidence interval [CI], 0.720–0.904), better performance than random forest (AUROC, 0.801; 95% CI, 0.708–0.890), logistic regression (AUROC, 0.802; 95% CI, 0.721–0.878), artificial neural net (AUROC, 0.736; 95% CI, 0.650–0.821), and conventional Morse fall score (AUROC, 0.652; 95% CI, 0.570–0.715). The model's interpretability was enhanced at both the population and patient levels. The algorithm was later integrated into the current EMR system.

Conclusion We developed an interpretable machine learning prediction model for inpatient fall events using EMR integration formats.

Keywords Accidental falls; Machine learning; Patient safety; Nursing informatics

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Capsule Summary

What is already known

Conventional scores such as the Morse Fall Scale are used for fall risk assessment; however, they have low accuracy and pose difficulty in practical implementation. Previous machine learning studies have limitations in explainability for clinicians and nurses, known as the "black box problem." Another challenge is that previous models have not been well-prepared for electronic medical records integration for practical application.

What is new in the current study

We developed the interpretable machine learning model for prediction of falls and for integration into the electronic medical records system.

INTRODUCTION

Falls are one of the most frequently occurring adverse events in hospitalized patients,[1] extending hospital stays, increasing medical costs, and increasing disability and mortality.[2,3] In the United States, falls occur at a rate of 3.3 to 11.5 per 1,000 hospital days.[4] Among patient safety accidents in Korea, falls were reported most frequently over the past 5 years, accounting for 45% or more of such incidents, with more than two-thirds resulting in mild or more serious injuries.[5]

Nurses must assess patient fall risk and, if necessary, provide appropriate caution and education. According to the Joint Commission on Healthcare Organization Accreditation and the Korea Institute for Healthcare Accreditation, falls are critical incidents, and preventing falls must be highly prioritized as a hospital policy.[6,7] The Morse Fall Scale (MFS) is the most widely used fall risk assessment scale and is used along with other tools.[8]

The MFS focuses primarily on intrinsic factors that are related to individual factors such as history of falls or polypharmacy,[9] and it poses major limitations in two aspects. First, the prediction accuracy of MFS varies significantly among healthcare settings and patient groups,[10,11] complicating its application due to the need for real-time intervention to respond to changing patient conditions. Second, because the MFS does not focus on individual risk factors,[12] nurses must apply a broad fall prevention plan without necessarily focusing on individual patient risk factors.

Advances in data science have contributed to the development of accurate fall risk prediction models; other studies created ensemble models or extreme gradient boosting models and identified significant predictors such as low self-care ability, sleep disorders, and medication use.[13,14] Though with acceptable accuracy, previous machine learning (ML) studies have limitations in their explainability for clinicians and nurses, which is also called the "black box problem." Another challenge is that previous models have not been well-prepared for electronic medical record (EMR) integration for practical application.[15,16]

To solve these limitations, the authors developed a model for predicting falls using interpretable ML and integrating the model into the EMR system to perform nursing interventions for each risk factor.

METHODS

Ethical statements

The study was approved by the Institutional Review Board of Samsung Medical Center (No. SMC 2022-03-052-001). Because of the retrospective nature of the study, the need for participant consent was waived.

Study setting

This retrospective study was conducted in Samsung Medical Center, a tertiary academic hospital in Seoul, Korea. The hospital had approximately 2,000 inpatient beds. Patient data from six general medical surgical wards with frequent fall reports were collected. Data were obtained from the EMRs. The TRIPOD (Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis) statement was followed for development and reporting of multivariable prediction models.[17]

Study population

All patients who were admitted to the six general wards from January 2018 to March 2020 were included in the study. Patients aged <18 years, those who had a length of stay <24 hours, and those with multiple fall injuries during the same admission were excluded. If patients were admitted more than once, each admission was evaluated independently. These admissions were split into two nonoverlapping cohorts for temporal validation: a development cohort from January 2018 to December 2019 and a test-

ing cohort from January 2020 to March 2020 for evaluation of the model.

Candidate predictors

Eighty-three candidate predictors were originally suggested based on a conceptual model of inpatient fall risk concepts from multiple national fall prevention guidelines in the United States and Korea.[18] Demographic and admission data, physician orders, and nurse records were selected as potential predictors. These variables were collected from patient data in the EMR via flowsheets, medical diagnoses, nursing care plans, and free-text notes. In previous studies, nurse intervention for fall prevention was reported to be an important variable[18,19] in the occurrence of falls, and a nursing care plan was used in this study. Here, as shown in Fig. 1, each candidate predictor was defined within 24 hours from admission with a 1-hour timeframe for predicting number of falls every hour.

Each circle represents a candidate predictor, and the number of circles is how many times the predictor was measured within 24 hours. The first prediction result can be calculated 24 hours after admission, defined as prediction index time.

For practical application by clinical providers, these 83 candi-

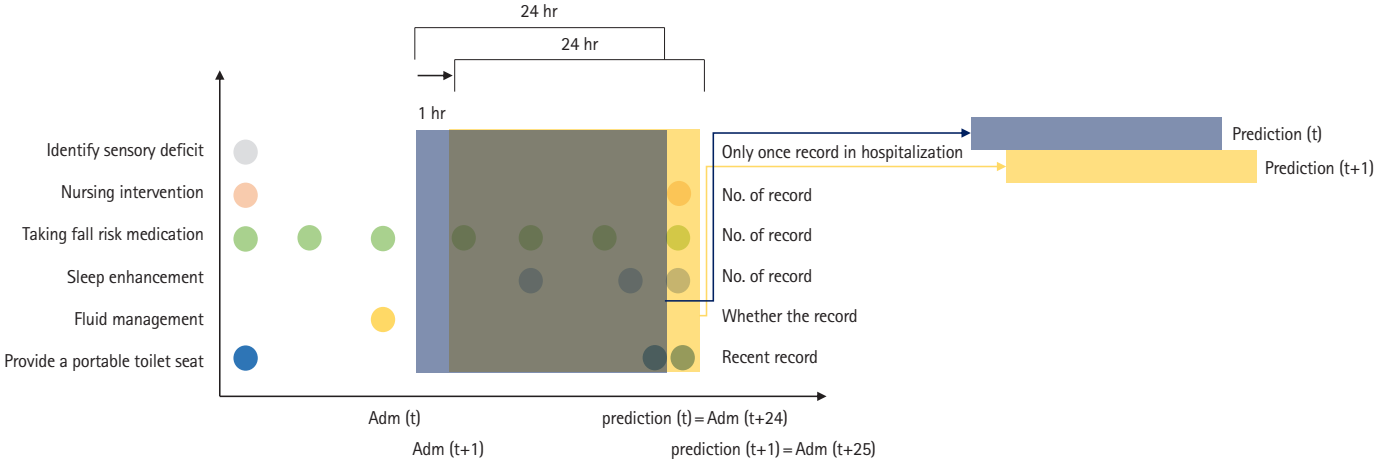

Fig. 1. Dataset generation for each variable from one admission. The time window was defined with 24 hours from the admission time and regenerated every 1 hour with updated value.

Table 1. Detailed list of candidates, known clinically significant predictors, and the seven categorized classes

Category	Count	Predictor
Universal	25	Age[a], sex[a], primary and secondary medical diagnoses[a], medical department[a], history of falls[a], length of stay[a], KPCS[a], number of medications[a], move-in date, dates of surgical operation
Cognitive function	11	Nursing assessment: mental status[a], RASS[a] Nursing diagnosis: acute chronic confusion[a] Nursing intervention: provide bed alarm with bed sensor pad[a], restraint
Toileting problem	7	Nursing intervention: timed voiding[a], portable toilet seat[a], medication (diuretics, laxative)[a] Nursing assessment: urine output, stool count Nursing diagnosis: impaired urination, diarrhea
Mobility problem	22	Nursing intervention: assistive device[a], fluid management[a] Nursing assessment: dizziness[a], activities of daily living, aid, deformity, disability, nursing diagnosis: impaired mobility
Medication	10	Fall risk medication (sedatives, antidepressants, antiemetics, antipsychotics, antianxiety drugs, antihypertensives, analgesics, antiarrhythmics and NSAIDs)[a] Nursing assessment: catheter (central venous line and intravenous line), adverse drug reaction monitoring
Sensory function	4	Nursing assessment: sensory, motor, circulation Nursing diagnosis: sensory perception Nursing intervention: assistive device
Sleep disturbance	4	Nursing assessment: sleep pattern, delirium Nursing diagnosis: disturbed sleep pattern Nursing intervention: sleep enhancement, medication (antianxiety drugs)

KPCS, Korean Patient Classification System; RASS, Richmond Agitation Sedation Scale; NSAID, nonsteroidal anti-inflammatory drug.
[a]Known clinically significant variable.

date predictors were mapped into seven categories of universal, cognitive function, defecation problems, mobility problems, medication, sensory function, and sleep disturbance according to "Evidence based clinical nursing practice guideline of Korea Hospital Nurses Association."[20] The list of predictors with known clinical and statistical significance in the model is presented in Table 1. Nursing assessments and interventions frequently were recorded for each shift, and the records of initial nursing evaluation at the time of admission were used. In addition, the Korean Patient Classification System (KPCS) score, which is recorded for inpatients every day, was also used. The predictor with the highest contribution was nursing intervention.

Outcomes of prediction models

Two distinct sources were used to collect primary outcomes for predicting falls. One was an incident reporting system. The other was regular expression of 11 fall-related terms, such as "fallen" and "slipped," from a free-text nursing record. Fall events were manually crosschecked by two nurses.

Statistical analysis

For statistical analysis, Python ver. 3.6.0 (Python Software Foundation, Wilmington, DE, USA) and SQL ver. 3.6.6 were used. Continuous variables were described as mean and standard deviation. Categorical variables were described as frequency and percentage. The t-test and chi-square test were used to calculate the P-value, and $P < 0.05$ was considered statistically significant.

The development cohort was used to develop the prediction model, and the testing cohort was used to optimize the hyperparameter. Then, the performance metrics of the final model were calculated based on the testing cohort.

During the analysis, missing values for KPCS score and fluid management were imputed with the most recent nonmissing value; 0 was imputed for other missing count values.

ML models

Adapted from a previous pilot study that used the Bayesian network model derived from January 2017 to June 2018 and showed 0.93 area under the receiver operating characteristic (AUROC) performance, an eXtreme Gradient Boosting (XGBoost) model, was developed as a fast and scalable ML technique for tree-based ensemble models.

Hyperparameter tuning for XGBoost was conducted considering the grid search of maximum depth, number of estimators, and learning rate, with the highest AUROC performance in the 10-fold cross-validation set.

The AUROC and area under the precision-recall curve (AUPRC) in the validation datasets were calculated. To obtain 95% confi-

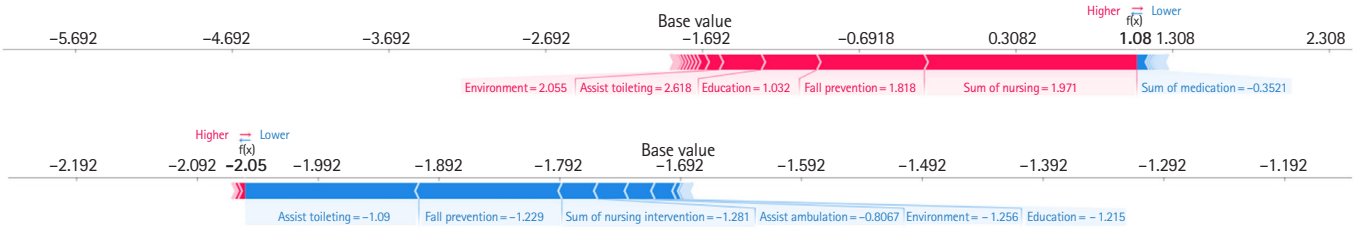

Fig. 2. Patient level example of SHAP force plot for individualized prediction result for fall prediction. Each value indicates the contribution of each feature for fall prediction; positive value represents positive contribution.

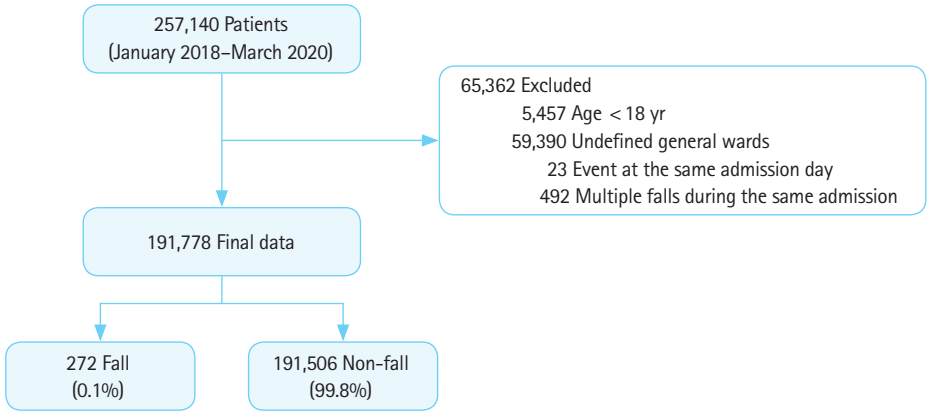

Fig. 3. Flowchart of the study.

dence intervals (CIs), 500 bootstrap repetitions were conducted. Sensitivity and specificity were calculated using the Youden index, which is defined as the point nearest the upper left corner of the ROC curve.

The prediction models were compared with the conventional point-based MFS, which consists of six evaluation items of history of falling, secondary disease, ambulatory aid, intravenous therapy/heparin lock, gait, and mental status[21] with and without nurse judgment. To supplement the MFS, the hospital identified high-risk individuals based on clinical judgments by the nurse.

Furthermore, other traditional ML methods were used for comparison. L2 regularized logistic regression, random forest, and essential artificial neural network (three layers) were performed with default settings. The software packages implemented for model development and validation were Python ver. 3.8.5, TensorFlow ver. 2.3.1, and scikit-learn ver. 0.23.2.

Model explainability for EMR integration

To apply the ML model to the clinical environment, the same model structure was developed for EMR integration. Seven categorized contributing factors to falls were identified at the patient level using the Shapley value, which has been widely used in game theory literature for calculating the contribution of each player in the game.[22] In terms of prediction modeling area, the Shapley value can be used to compute the contribution of each data point to the model's final performance and can be visualized with the SHAP force plot as shown in Fig. 2. The ML model, which suggests patient risk factors according to the Shapley value, was integrated into the EMR, and screen development was implemented for actual clinical settings.

Two components, the predictive probability of falls and the predictive risk factor, were presented on the EMR screen. According to the set threshold, the patient was classified as high or low risk, and the top three categorized feature contributions were selected for the preceding intervention. If the patient was classified as low risk but the nurse did not agree, a rating of high risk was allowed. If the nurse agreed on the predictive result and the risk

Table 2. Basic characteristics of the study population

Characteristic	Fall (n = 272)	No fall (n = 191,506)	P-value
Age (yr)	62.1 ± 14.6	59.8 ± 14.2	0.012
Sex			0.944
Male	167 (61.4)	116,830 (61.0)	
Female	105 (38.6)	74,676 (39.0)	
Length of stay (day)	18.9 ± 21.6	23.5 ± 160.5	0.001
Korean Patient Classification System			< 0.001
Group 1 (less severe)	46 (16.9)	43,676 (22.8)	
Group 2	165 (60.7)	82,514 (43.1)	
Group 3	48 (17.6)	31,886 (16.7)	
Group 4 (most severe)	12 (4.4)	11,235 (5.9)	
Null	1 (0.4)	22,195 (11.6)	
Daily medications per person (past 4 wk)	21.3 ± 28.3	15.9 ± 37.9	0.002
Patient classification			0.219
Surgical	83 (30.5)	63,873 (33.4)	
Medical	189 (69.5)	127,633 (66.6)	

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

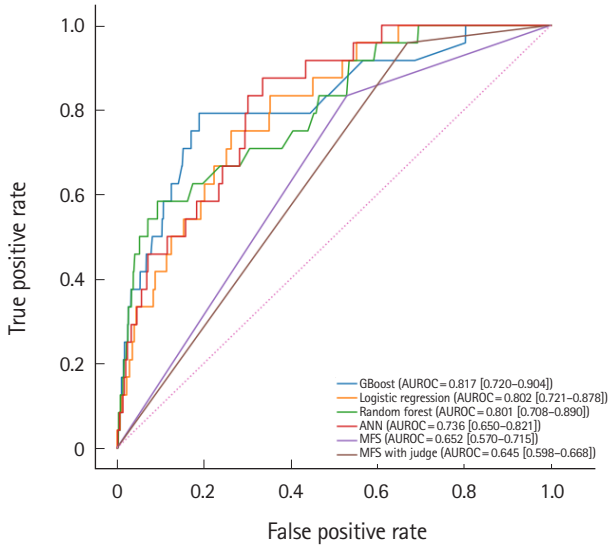

Fig. 4. Comparison of area under the receiver operating characteristic (AUROC) curves for gradient boost model (GBoost), logistic regression, random forest, artificial neural network (ANN), Morse Fall Scale (MFS), and MFS with judgement.

Table 3. Comparison of evaluation values with 95% CI achieved by different methods in the testing cohort

Variable	AUROC (95% CI)	AUPRC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Gradient boost model	0.817 (0.720–0.904)	0.010 (0.005–0.022)	0.750 (0.579–0.909)	0.811 (0.805–0.816)
Random forest	0.801 (0.708–0.890)	0.010 (0.005–0.026)	0.542 (0.350–0.737)	0.907 (0.903–0.911)
Logistic regression	0.802 (0.721–0.878)	0.011 (0.003–0.055)	0.708 (0.500–0.889)	0.736 (0.730–0.742)
Artificial neural network	0.736 (0.650–0.821)	0.008 (0.002–0.040)	0.750 (0.583–0.909)	0.640 (0.633–0.647)
MFS	0.652 (0.570–0.715)	0.004 (0.002–0.010)	0.833 (0.684–0.960)	0.470 (0.463–0.477)
MFS with judgement	0.645 (0.598–0.668)	0.002 (0.001–0.003)	0.958 (0.867–1.000)	0.331 (0.324–0.337)

CI, confidence interval; AUROC, area under the receiver operating characteristic; AUPRC, area under the precision-recall curve; MFS, Morse Fall Scale.

factors, the recommended intervention was performed and analyzed. When a low-risk patient became a high-risk patient, a pop-up on the screen informed the nurse of the status change.

RESULTS

Basic characteristics

Initially, 257,140 cases between January 2018 and March 2020 were included. A total of 65,362 cases was excluded due to age younger than 18 years, admission to an undefined general ward, events occurring on admission day, or multiple falls during the same admission. A total of 191,778 cases (272 cases [0.14%] in the group with falls) was used for the final data analysis. The flow diagram of the study process is shown in Fig. 3.

Basic characteristics of patients are listed in Table 2. During the study period, 272 fall cases (0.14%; mean age ± standard deviation, 62.1 ± 14.6 years; male patients, 167 [61.4%]) were reported. There were more male and elderly patients in the fall group and patients were more likely to take medication and have a secondary diagnosis.

ML models

An ML-based fall prediction algorithm was developed. Table 3 summarizes the AUROC, AUPRC, and other metrics using various

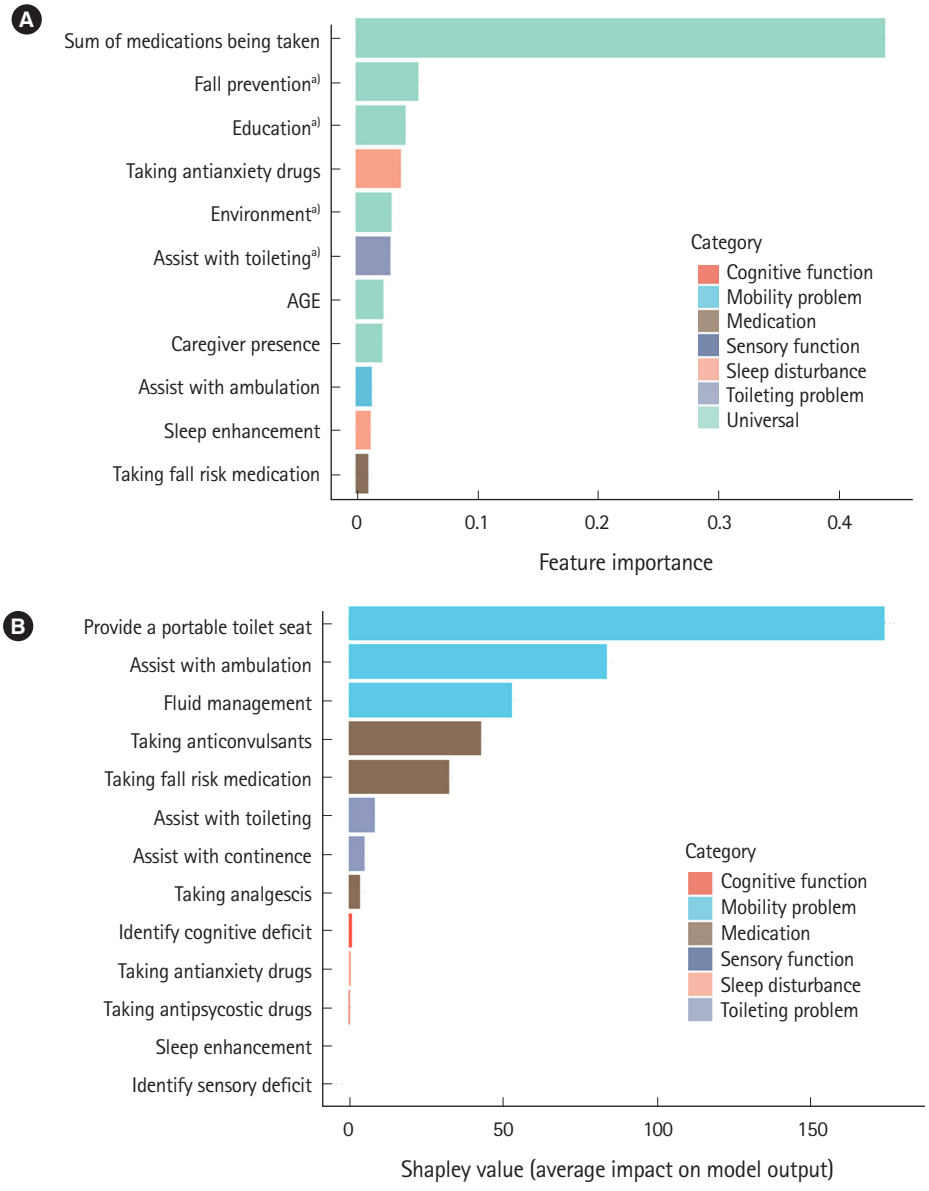

Fig. 5. Population-level and patient-level interpretations for fall events. (A) Population-level interpretation with feature importance by gradient boosting. (B) Patient-level interpretation with Shapley value. [a]Nursing intervention.

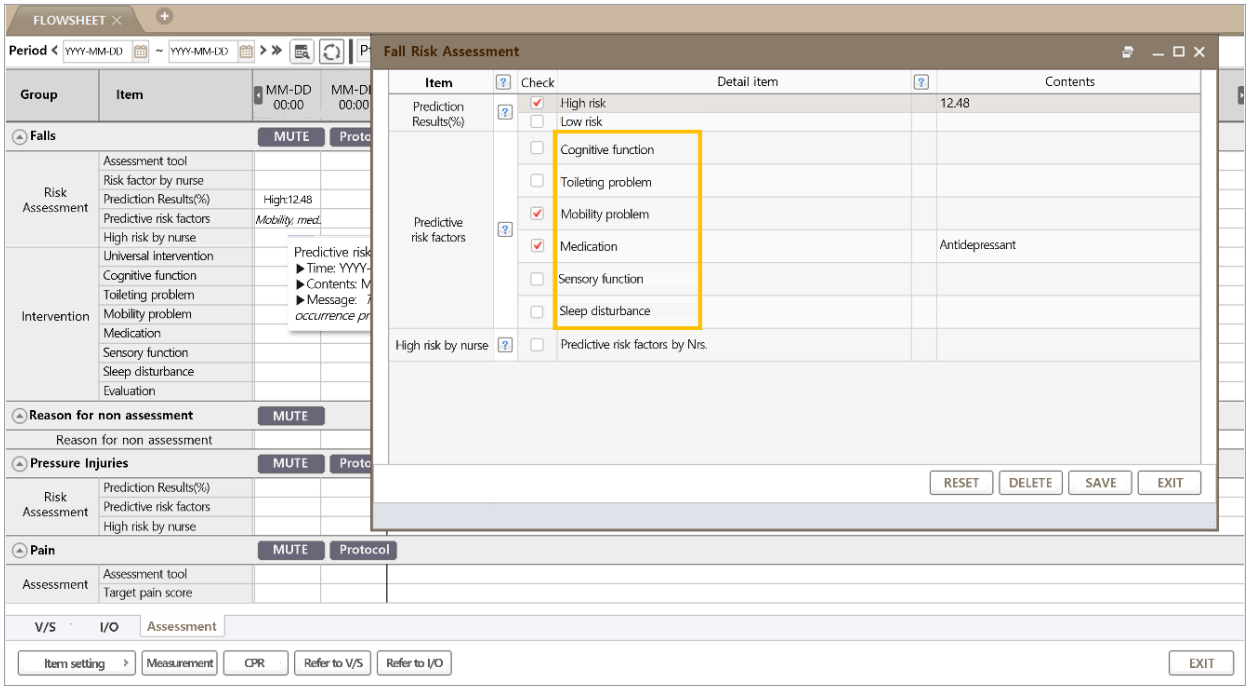

Fig. 6. Clinical decision support system of the fall prediction model in the electronic medical records. In the bold yellow box, the patient-level, top two contributing factors are automatically checked (red check marks) from six categorized predictors.

methods with 95% CI. The best AUROC and AUPRC were 0.817 (95% CI, 0.720–0.904) and 0.010 (95% CI, 0.005–0.022), respectively, for the gradient boost model. The AUROC plot is shown in Fig. 4.

According to the cutoffs determined by the Youden index, the sensitivities (95% CI) of the gradient boost model, random forest, logistic regression, artificial neural network, MFS, and MFS with judgement 0.750 (0.579–0.909), 0.542 (0.350–0.737), 0.708 (0.500–0.889), 0.750 (0.583–0.909), 0.833 (0.684–0.960), and 0.958 (0.867–1.000), respectively; and the specificities (95% CI) were 0.811 (0.805–0.816), 0.907 (0.903–0.911), 0.736 (0.730–0.742), 0.640 (0.633–0.647), 0.470 (0.463–0.477), and 0.331 (0.324–0.337), respectively.

The contribution of the event to the seven categorized factors was identified in terms of population and patients, as shown in Fig. 5. Number of medications taken, number of nursing interventions for fall prevention, and education were the most influential factors in predicting falls at the population level.

Regarding the patient-level prediction, as shown in Fig. 5B, patient risk was demonstrated using individual factors and their Shapley values. The patient-level predictors are displayed in the EMR (Fig. 6). The reason for positive fall prediction was displayed as a binary output (checkbox) of cognitive function, toileting problems, mobility problems, medication, sensory function, and sleep disturbance.

DISCUSSION

In this study, an interpretable ML for fall event prediction was developed using 83 predictors from EMR data, with the gradient boost model demonstrating the highest performance. Predictors were categorized as fall risk factors and incorporated into the EMR. This can be the cornerstone for development of an artificial intelligence (AI)-based clinical decision support system (CDSS) for application to the clinical field.

Patients in this study who experienced falls tended to be older, were hospitalized longer, and used more medications. These results are consistent with the characteristics of patients at risk for falls.[14,18] All these characteristics were used as significant predictors.

The model performance of this study was AUROC 0.817, which was higher than that of previous studies.[13,14] Medication and nursing intervention were important predictors, consistent with a previous study.[18] Lower limb weakness and dysuria were the strongest predictors in previous studies[14,19]; assistance toileting and ambulation nursing interventions also were high predictors and were similarly consistent. Another study showed that admission data were high in feature importance, but they input more variables to reflect specific patient conditions.[14] The present study developed a model including formally reported falls as well as falls that were recorded only in clinical notes. Data that reflect patient status at the time of a fall were used based on a previous

study.[19] Using these, the model sensitivity and specificity could be improved for model accuracy and for accuracy in clinical application settings.

Interpretable ML is critical for nursing practice application.[23,24] Accuracy and actionable intervention are important in the case of in-hospital falls as they might result in lawsuits. The findings of this study will enable identification of risk factors that can guide individualized interventions in fall prevention.

Although many ML algorithms have been developed to predict falls, pressure injuries, and delirium,[13,23,25] there has been no study that is integrated with and applied to the actual EMR. Prospective studies could be evaluated to determine the applicability and usefulness of AI-based CDSS for future studies.

AI for patient safety is a very impactful and effective area of study and practice. AI can be extended as a valuable tool to improve patient safety in multiple clinical settings including healthcare-associated infections, adverse drug events, venous thromboembolism, surgical complications, pressure ulcers, falls, decompensation, and diagnostic errors.[24]

This study had some limitations. First, the study was performed in a single center in a retrospective manner. To verify model performance, further large clinical datasets and multicenter validation are required. Prospective studies could be evaluated to verify the algorithm performance with the CDSS, which involves evaluation of its effectiveness and usability in work processes and safety outcomes.

Second, in terms of predictors, the dataset used in this study was based on routinely collected EMR variables. Thus, other factors such as environmental and behavioral conditions, which are important but not often recorded in the EMR, could not be utilized.

Finally, fall outcomes were collected only through EMR reports. Near-miss cases such as stumbling and sliding, which had not been reported or recognized by providers, have potential importance. Further studies should involve sensors and patient reports about such cases.

In conclusion, the present study developed an interpretable ML prediction model for fall events that was integrated into the EMR. This study is one of the first attempts to integrate AI-CDSS into practice on a large scale, and further studies are needed regarding effectiveness and safety.

CONFLICT OF INTEREST

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

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AUTHOR CONTRIBUTIONS

Conceptualization: SH; Data curation: SJ, YJS, KTM; Formal analysis: SJ, YJS, KTM; Investigation: SS, JYY, JHL, KMY, SHP, ISC, MRS, JHH; Methodology: SJ, YJS, KTM; Visualization: SS, JYY, SJ, YJS, KTM; Writing–original draft: SS, JYY, SH; Writing–review & editing: SS, JYY, SH, JHL, KMY, SHP, ISC, MRS, JHH.
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Original Article

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Comparison of emergency department workloads before and during the COVID-19 pandemic as assessed using relative value units

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Objective This study aimed to assess and compare emergency department (ED) workloads by using relative value units (RVUs) before and during the COVID-19 pandemic.

Methods This retrospective observational study investigated the RVUs of a single ED from 2019 to 2021. We calculated the mean number of patients per day (PPD) for each year and selected the days when the number of patients was equal to the yearly mean PPD for each of the three years. We calculated the total RVUs per day and RVUs per patient and compared them.

Results We analyzed the RVUs of 12 days in 2019 (mean PPD, 88), 10 days in 2020 (mean PPD, 75), and 14 days in 2021 (mean PPD, 83). The mean of the total RVUs per day were as follows: 533,057.5±66,239.1 in 2019, 505,994.6±48,935.4 in 2020, and 634,219.6±64,024.2 in 2021 ($P<0.001$). The RVUs per patient in the three year-groups were significantly different (6,057.5±752.7 in 2019, 6,746.6±652.5 in 2020, and 7,641.2±771.4 in 2021; $P<0.001$). Post hoc analyses indicated that the total RVUs per day and the RVUs per patient in 2021 were significantly higher than in 2019 or 2020, although the mean PPD in 2019 was the highest.

Conclusion Since the onset of the COVID-19 pandemic, the mean RVUs per patient have increased, suggesting that the workload per patient may also have increased in the regional emergency medical center.

Keywords Emergency medical services; COVID-19; Relative value scales; Workload

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CEEM

Capsule Summary

What is already known

It is essential to accurately assess the workload of emergency departments (EDs). Measuring the workload can facilitate appropriate resource allocation to provide quality emergency medical care. There were studies to measure workload using relative value units (RVUs) in other non-ED areas of hospitals outside of Korea.

What is new in the current study

This study showed that since the COVID-19 pandemic, the mean RVU per patient has increased, suggesting that the workload per patient may also have increased in the regional emergency medical center. Moreover, there were considerable differences between the actual workload that estimated using RVUs and the number of patients in the ED.

INTRODUCTION

It is essential to accurately assess the workload of emergency departments (EDs). Measuring the workload properly can facilitate appropriate resource allocation to provide quality emergency medical care. However, the ED is an environment where many patients with various medical complaints and needs are seen every day. The workload varies depending on the patient.[1,2] Thus, the actual workload performed by an emergency physician (EP) may not match the number of patients they see.

Several studies have been conducted to measure the workload of EDs. A study conducted in Australia attempted to measure ED workload using newly developed emergency care workload units composed of measurements of patient capacity, disposition, numbers of patients, and the individual cost of each presentation.[3] In a British study, there was an attempt to directly observe and record EP activities of each moment (e.g., history taking, physical examination, clinical skills, etc.) to estimate the amount of EP time required.[4] However, each of the existing models of ED workloads has significant limitations.[5]

In other hospital areas or functions, attempts have been made to measure workload using relative value units (RVUs).[6] In brief, RVUs are a measure of value used in the typical formula to calculate compensation for physician services, which vary from country to country. An RVU is designed to value physicians' service and serve as a guide for reimbursement, and can be applied to assess the productivity, cost, and benchmarking of medical services.[7] The advantage of using RVUs to measure workload is that it is possible to directly assign a numerical value to the procedures performed on the patients. For example, the RVU for central venous catheterization in Korea is 1,124.7, and the value is identical in all hospitals. However, in the compensation claim, this value is multiplied by a predetermined ratio that varies according to the level of hospital (third hospital vs. private clinic), the situation (day vs. night), and the patients treated (adult vs. pediatrics). We postulated that there have been changes in the workload performed per patient visiting the ED after the onset of the COVID-19 pandemic. However, to date, no studies have used RVUs to assess and report the workload of EDs in Korea. Therefore, this study aimed to use RVUs to evaluate and compare the identify workload of an ED in an academic hospital. Specifically, the purpose of this study was to calculate the difference between RVUs per patient and compare the total RVUs per day before and during the COVID-19 period for days on which the mean number of patients visiting the ED was equal to annual mean number of patients seen per day.

METHODS

Ethical statements

The study was approved by the Institutional Review Board of Dong-A University Hospital (No. DAUHIRB-EXP-22-03). Informed consent was waived due to the anonymous nature of the data.

Study design and setting

This retrospective observational study investigated and compared the RVUs in a single ED from 2019 to 2021. We calculated the mean number of patients per day (PPD) for each year and selected the days when the number of patients was equal to the yearly mean PPD for each of the three years. We calculated the total RVUs and RVUs per patient on those days and compared them (Fig. 1). We postulated that the ED would experience average working patterns on the selected days when an average number of patients visited the ED.

This research was performed at an urban academic medical center with an 830-bed hospital. There were six members of the

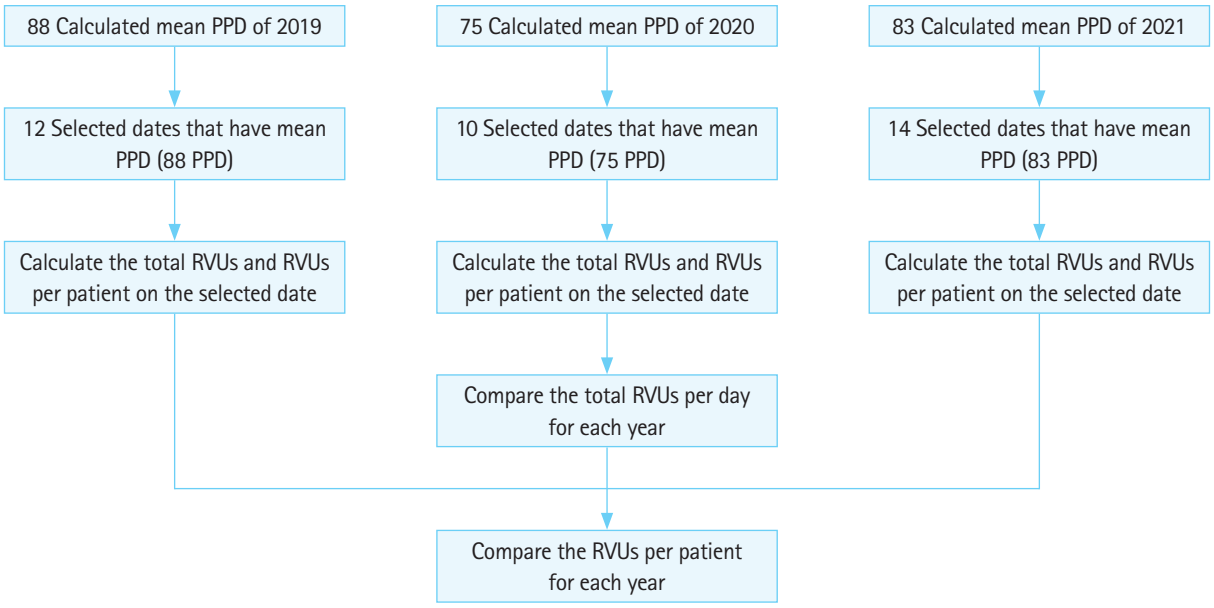

Fig. 1. Flow chart of the study design. PPD, patients per day; RVU, relative value unit; SD, standard deviation.

teaching staff and four emergency medicine residents. In 2017, this ED was designated as a regional emergency medical center. Approximately 32,000 patients visit the ED annually. The 3-year average percentage of cases that scored 3 or higher on the Korean triage and acuity scale (KTAS) was approximately 59.3%. The hospitalization rates in the ward and intensive care unit were about 35.5% and 9.5%, respectively.

Study outcomes

The primary objective was to compare the difference between the RVUs per patient in the year prior to and during the first two years of the COVID-19 pandemic on days when the mean number of PPD was equal to the annualized mean for each of the three years. The secondary objective was to compare total RVUs on days with the same mean number of PPD for each year.

Data source and collection

The RVUs are calculated automatically by the program when a physician inserts a prescription into the electronic medical record program. The data were collected through the hospital insurance department and subsequently downloaded to Microsoft Excel (Microsoft Corp., Redmond, WA, USA).

Statistical analysis

Descriptive statistics for the RVU data for those days with the same PPD as the mean PPD per year were compiled, including the mean, standard deviation, maximum, and minimum. The comparison of the daily RVUs per patient each year was conducted using a one-way analysis of variance. Post hoc analyses were conducted using the Tukey test. All the tests were two-tailed, and P-values less than 0.05 were considered statistically significant. All statistical analyses were performed using Microsoft Excel and R ver. 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Comparison of total RVUs for the selected days when the number of patients seen was equal to the annualized mean number of PPD

During the study period, the mean PPD was 88 in 2019, 75 in 2020, and 83 in 2021. There were 12 days in 2019 when 88 patients visited the ED, 10 days in 2020 when 75 patients visited, and 14 days in 2021 when 83 patients visited. The mean PPD in three year-groups was significantly different ($P<0.001$). Post hoc analysis was for 2019 and 2020 ($P<0.001$), 2020 and 2021 ($P=0.026$), and 2019 and 2021 ($P=0.116$). The mean of the total RVUs for the selected days with the same PPD as the yearly mean PPD were as follows: 533,057.5±66,239.1 in 2019, 505,994.6±48,935.4 in 2020, and 634,219.6±64,024.2 in 2021 (Table 1). The means of the total RVUs in the three year-groups were significantly different ($P<0.001$). Post hoc analyses for 2019 and 2020 ($P=0.034$), 2019 and 2021 ($P<0.001$), and 2020 and 2021 ($P=0.007$) were significantly different. The mean PPD was higher in 2019 than in 2021 (88 PPD vs. 83 PPD, $P=0.116$), but the mean total RVUs was higher in 2021 than in 2019 ($P<0.001$).

Table 1. Comparison of the total RVUs on days when the number of patients seen in the emergency department was equal to the mean number of patients seen per day for each year

No. of date	2019 (n=88)[a]			2020 (n=75)[a]			2021 (n=83)[a]		
	Date[b]	Total RVUs	RVUs per patient	Date[b]	Total RVUs	RVUs per patient	Date[b]	Total RVUs	RVUs per patient
1	2019-01-08	585,392.5	6,652.2	2020-02-28	416,295.9	5,550.6	2021-01-15	675,341.6	8,136.7
2	2019-02-02	588,908.7	6,692.1	2020-04-20	521,776.2	6,957.0	2021-02-14	600,313.5	7,232.7
3	2019-02-12	613,561.9	6,972.3	2020-05-10	502,745.1	6,703.3	2021-02-15	592,423.4	7,137.6
4	2019-02-22	603,730.1	6,860.6	2020-05-11	463,783.3	6,183.8	2021-02-27	547,860.2	6,600.7
5	2019-02-24	532,278.9	6,048.6	2020-06-05	493,956.6	6,586.1	2021-04-08	618,529.8	7,452.2
6	2019-03-10	460,497.0	5,233.0	2020-09-04	550,201.4	7,336.0	2021-04-27	722,040.6	8,699.3
7	2019-04-25	474,307.8	5,389.9	2020-11-12	484,569.6	6,460.9	2021-06-04	612,598.0	7,380.7
8	2019-06-01	438,469.1	4,982.6	2020-12-01	593,509.4	7,913.5	2021-07-17	570,314.4	6,871.3
9	2019-06-16	435,801.0	4,952.3	2020-12-05	539,190.3	7,189.2	2021-07-28	722,316.0	8,702.6
10	2019-07-15	523,051.8	5,943.8	2020-12-23	493,918.2	6,585.6	2027-09-02	611,532.9	7,367.9
11	2019-08-19	591,863.7	6,725.7	-	-	-	2021-11-23	617,543.4	7,440.3
12	2019-10-19	548,827.8	6,236.7	-	-	-	2021-11-27	581,233.1	7,002.8
13	-	-	-	-	-	-	2021-11-29	765,835.8	9,226.9
14	-	-	-	-	-	-	2021-12-07	641,191.3	7,725.2
Mean		533,057.5	6,057.5		505,994.6	6,746.6		634,219.6	7,641.2
SD		66,239.1	752.7		48,935.4	652.5		64,024.2	771.4
Minimum		435,801.0	4,952.3		416,295.9	5,550.6		547,860.2	6,600.7
Maximum		613,561.9	6,972.3		593,509.4	7,913.5		765,835.8	9,226.9
95% CI upper		570,535.1	6,483.4		536,324.5	7,151.0		667,756.9	8,045.3
95% CI lower		495,579.9	5,631.6		475,664.7	6,342.2		600,682.2	7,237.1

RVU, relative value unit; SD, standard deviation; CI, confidence interval.

[a]Mean patients per day in each year. [b]Selected dates are the days the number of patients admitted to the emergency department was equal to the mean patients per day in each year. The mean patient per day in the three year-groups was significantly different ($P<0.001$). Post hoc analyses were for 2019 and 2020 ($P<0.001$), 2020 and 2021 ($P=0.026$), and 2019 and 2021 ($P=0.116$). The mean of the total RVUs in the three year-groups was significantly different ($P<0.001$). Post hoc analyses were for 2019 and 2020 ($P=0.034$), 2020 and 2021 ($P=0.007$), and 2019 and 2021 ($P<0.001$). The RVUs per patient for the three year-groups were significantly different ($P<0.001$). Post hoc analyses indicated the RVUs for 2019 and 2021 ($P<0.001$) and for 2020 and 2021 ($P<0.001$) were significantly different, but the RVUs for 2019 and 2020 ($P=0.560$) were not significantly different.

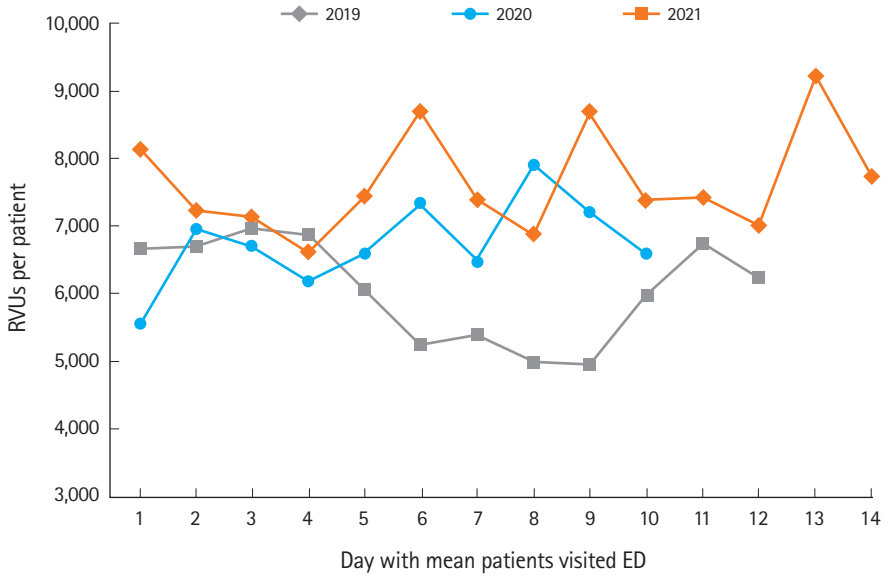

Fig. 2. Comparison of relative value units (RVUs) per patient on days with the same number of patients as the mean patients per day for each year. The X-axis indicates the day when the mean number of patients per year visited the emergency department (ED), and the Y-axis indicates the RVUs per patient for that day.

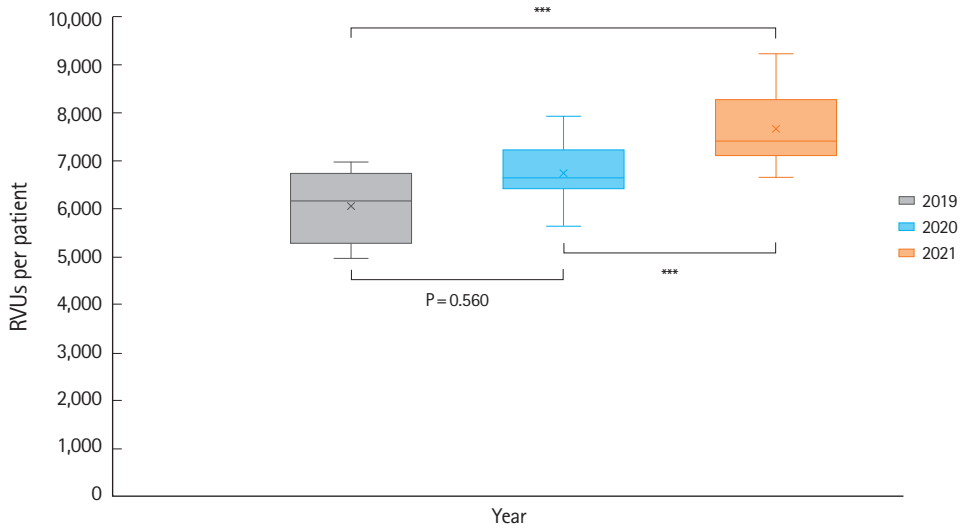

Fig. 3. Comparison of relative value units (RVUs) per patient on days with the same number of patients as the mean patients per day for each year with boxplots. The boxplot shows the maximum, third quartile, median, first quartile, and minimum from the upper line to the lower line, and the X mark indicates the mean. ***P<0.001.

Comparison of RVUs per patient on the days with the same mean number of PPD

The daily RVUs per patient are presented in Table 1 and Figs. 2 and 3. Since the onset of the COVID-19 pandemic, the RVUs per patient has increased. The RVUs per patient in the three year-groups were significantly different (6,057.5±752.7 in 2019, 6,746.6±652.5 in 2020, and 7,641.2±771.4 in 2021; P<0.001). Post hoc analyses of the RVUs for 2019 and 2021 (P<0.001) and 2020 and 2021 (P<0.001) were significantly different, but the RVUs for 2019 and 2020 (P=0.560) were not significantly different.

DISCUSSION

The goals of this study were to estimate the total workload using RVUs and examine changes in the RVUs per patient since the COVID-19 pandemic began. The mean PPD was higher in 2019 than in 2021 (88 PPD vs. 83 PPD), but the mean total RVUs was higher in 2021 than in 2019. The RVUs per patient have been steadily increasing during the COVID-19 pandemic.

There has been some controversy regarding the use of RVUs in the measurement of physician performance or workloads. The use of RVUs was initially designed to provide relative economic values of healthcare services based on the cost of delivering services, including costs attributed to physician's work, medical expenses, and professional liability.[8] It should be noted that RVUs were not originally intended to function as the primary measure of a physician's performance. Thus, assessing physician performance by RVUs monetizes the patient-physician relationship and incentivizes more, although not necessarily better, care.[9] The use of RVUs also indirectly discourages clinicians from focusing on essential behaviors to improve outcomes and reduce costs.[10] In addition, RVU assignments correlate poorly with specific metrics of surgical work.[11] High productivity does not always reflect the intensity of work. Nevertheless, the practice of using RVUs to measure workload or productivity is widespread, as RVUs are used globally as a standardized metric to describe medical services.[12] If RVUs are used as a tool of reward to physicians, physicians may prefer skills or treatment with high RVUs. However, emergency care in the ED is not performed for compensation, and EPs in Korea are also not compensated based on the RVUs. Thus, it is thought that there will be no exaggeration in estimating the workloads with RVUs.

Few studies in Korea have used RVUs to estimate workload or productivity. Most studies have investigated whether the RVU of a specific procedure or surgery is adequately valued or reimbursed. One study that analyzed changes in spinal surgery and intervention reported that RVUs for more complex spinal and brain neurosurgery procedures increased by 125.3% and 133%, respectively, during the same period.[13] Another study examined associated physician fees and used RVUs to compare the mean proportion of the total medical cost represented by physician labor costs: the resulting value of 0.19 was significantly lower than that for corresponding procedures in the United States based on RVUs (mean, 0.48).[14] One reason RVUs have not been used to estimate workload or productivity in Korea may be because this system is not directly linked to physician wages.

Studies comparing workload using RVUs are relatively common in the United States. This is because RVUs were developed to reimburse physicians based on their workload. A study in the United

States reported that an approximately 60% reduction in workloads in the radiology department after COVID-19 was reported when using RVUs, and this information was used for staff redeployment.[15] Another study described the financial impact of COVID-19 on an academic neurosurgery department using daily RVUs and found that the mean reduction was 51.4% compared with the pre-COVID period.[16] However, we could not find any studies from Korea that reported changes in RVUs before and after the onset of the COVID-19 pandemic.

In our study, the mean PPD in the ED decreased after the COVID-19 pandemic began, but RVUs per patient increased. These findings are consistent with a study by Pines et al.,[17] wherein the authors found that following the onset of the COVID-19 pandemic, geriatric, adult, and pediatric visits declined by 43%, 40%, and 73%, respectively, compared to 2019. However, RVUs per visit rose by 8%, 9%, and 18%, respectively. This finding may be partly attributed to the use of additional diagnostic procedures, such as chest computed tomography or COVID-19 polymerase chain reaction (PCR) tests, to screen patients for COVID-19. The COVID-19 PCR test in Korea is assigned 1,630.6 RVUs. It can be estimated that 24% of RVUs per patient in 2020 and 21% of RVUs per patient in 2021 were associated with COVID-19-related work in this study. Alternatively, the influence of COVID-19 on RVUs may be due to an increased proportion of more severely or acutely ill patients presenting to the regional emergency medical center requiring more complex procedures.[18] In the ED where this study was conducted, the proportion of emergency patients with KTAS scale of 3 or higher increased from 57.7% in 2019, to 58.3% in 2020, and 61.8% in 2021 during the study period, although it should be noted that the KTAS does not directly reflect the patient's severity or resource requirements.

The current standard staffing requirement for EDs in Korea is based on the number of patients visiting the ED per year. According to the criteria governing regional emergency medical centers, the rules for assigning EPs state that if the number of patients in the ED exceeds 30,000 in the previous year, a medical center will be added, and one additional EP per 10,000 patients will be secured.[19] The findings of our study confirm that when assigning ED staff, the number of patients may not sufficiently reflect the actual workload of the ED. The standards for staffing need to reflect the actual workload, and not only the number of patients, and in particular, need to consider the increase in the RVUs per patient due to COVID-19. We found the RVU reflects the ED workload better than patient numbers, but it is not sufficient. It is necessary to develop a new ED workload measurement tool, such as the emergency care workload units developed in Australia.[3]

We acknowledge that there are several limitations to our study. First, this study analyzed data from a single ED. Further analyses of data from several EDs with varying patient volume and context should be conducted. In the case of regional emergency medical institutions, where the number of patients visiting the ED decreased and the proportion of severely ill patients also decreased during the COVID-19 pandemic, the RVUs per patient would have been reduced as well. However, caution should be taken in using these results as a criterion for staff reduction. This is because emergency medical services serve as social safety nets. Second, features of medical services that could not be measured by RVUs, such as multitasking in the ED—treating multiple patients simultaneously—were not assessed in this study. Third, the RVUs of each procedure performed in the ED were not evaluated in depth. We did not evaluate whether the difference in RVUs between a surgeon suturing a patient's wound during the day and an EP suturing at midnight was appropriate. Productivity as evaluated by RVUs can change depending on the physician and patient, even for patients with similar complaints. In addition, if a specialist and a resident work together, it is not always easy to attribute the result to one or the other. Fourth, this study focused on the workload of an ED, and not on the workload of individual EPs; in a study by Park et al.[20] that evaluated the nonclinical work of EPs who worked in a training hospital, administrative and educational work was found to be a considerable burden over and above clinical work. Further research is required on this topic.

In conclusion, we provided an estimate of ED workload based on the number of patients treated. However, this study showed that there was a gap between the actual workload in the ED and the number of patients. Moreover, since the COVID-19 pandemic began, the mean RVUs per patient has increased, suggesting that the workload per patient may also increase in a regional emergency medical center. Estimating the ED workload is the basis for calculating staffing requirement and preparing adequate resources. When staff are assigned appropriately, safe and quality emergency medical services can be provided. It is time to consider measuring ED workload based on the actual amount of work performed and not only on the number of patients visiting the ED.

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: all authors; Formal analysis: all authors; Funding acquisition: SYP; Investigation: all authors; Methodology: all authors; Project administration: all authors; Resources: all authors; Software: all authors; Supervision: all authors; Validation: all authors; Visualization: all authors; Writing–original draft: all authors; Writing–review & editing: all authors.

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Study Protocol

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Augmented-Medication CardioPulmonary Resuscitation (AMCPR) trial: a study protocol for a randomized controlled trial

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Objective Clinical trials on demodynamic-directed cardiopulmonary resuscitation have been limited. The aim of this study is to investigate whether Augmented-Medication CardioPulmonary Resuscitation (AMCPR) would improve the odds of return of spontaneous circulation (ROSC) in patients with out-of-hospital cardiac arrest.

Methods This is a double-blind, single-center, randomized placebo-controlled trial that will be conducted in the emergency department of a tertiary, university-affiliated hospital in Seoul, Korea. A total of 148 adult patients with nontraumatic, nonshockable, out-of-hospital cardiac arrest who have an initial diastolic blood pressure above 20 mmHg will be randomly assigned to two groups of 74 patients (a 1:1 ratio). Patients will receive an intravenous dose of 40 IU of vasopressin with epinephrine, or a placebo with epinephrine. The primary endpoint is a sustained ROSC (over 20 minutes). Secondary endpoints are enhanced diastolic blood pressure, end-tidal carbon dioxide levels, acidosis, and lactate levels during resuscitation.

Discussion AMCPR is a trial about tailored medication for select patients during resuscitation. This is the first randomized control trial to identify patients who would benefit from vasopressin for achieving ROSC. This study will provide evidence about the effect of administration of vasopressin with epinephrine to increase ROSC rate.

Trial registration ClinicalTrials.gov identifier: NCT03191240. Registered on June 19, 2017.

Keywords Out-of-hospital cardiac arrest; Vasopressins; Cardiopulmonary resuscitation; Epinephrine

Capsule Summary

What is already known

A combination of vasopressin and epinephrine for patients with out-of-hospital cardiac arrest has shown not to improve outcomes.

What is new in the current study

We propose the Augmented-Medication CardioPulmonary Resuscitation (AMCPR) trial to determine whether the addition of vasopressin in refractory cardiac arrest patients with low diastolic blood pressure during cardiopulmonary resuscitation improves return of spontaneous circulation rate.

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INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) is a major public health burden contributing to morbidity and mortality worldwide.[1-3] A recent epidemiological study reported that over one in 10,000 patients suffered from cardiac arrest and survival rates were lower than 20%.[4] To improve outcomes, the guidelines of the American Heart Association and European Resuscitation Council have strengthened the chain of survival, including early recognition, effective chest compression, timely defibrillation, and prompt use of vasopressors.[5-7] Among various vasopressors, epinephrine and vasopressin have been considered as candidates to improve the chance of return of spontaneous circulation (ROSC).[8,9] Because vasopressin stimulates smooth muscles to vasoconstrict without a catecholamine effect, it can be used for patients with cardiac arrest by utilizing a different mechanism than with epinephrine.[10] However, current guidelines do not recommended vasopressin as a replacement for epinephrine (class III) based on previous research that additional use of vasopressin did not have any outcome benefit compared to epinephrine alone.[11-13] However, previous controlled trials did not observe real-time changes in diastolic blood pressure or end-tidal carbon dioxide levels, which are considered surrogate markers of organ perfusion.[11,12] Moreover, the effectiveness of vasopressin could be masked especially in patient with cardiac arrest who had sufficient response to conventional epinephrine doses for increasing vital organ perfusion.[13,14]

Although resuscitation guidelines remain uniform across all cardiac arrest patients, individualizing resuscitation to appropriate hemodynamic goals rather than using a standard "one-size-fits-all" cardiopulmonary resuscitation (CPR) seems a promising strategy in highly monitored patients. Previous randomized controlled animal studies established that hemodynamic-directed targeted CPR results in superior outcomes compared to standard CPR.[15-17] However clinical trials on hemodynamic-directed CPR have been limited. Therefore, individualization strategies, such as blood pressure-directed CPR including the administration of additional vasopressors in refractory cardiac arrest patients who cannot maintain diastolic blood pressure with epinephrine injection alone during CPR, may be useful.

The aim of the study is to determine whether the addition of vasopressin in refractory cardiac arrest patients during CPR improves ROSC rate. We therefore designed the Augmented-Medication CardioPulmonary Resuscitation (AMCPR) trial. We hypothesized that the addition of vasopressin when patients cannot achieve a diastolic blood pressure over 20 mmHg with epinephrine during CPR, would improve outcomes.

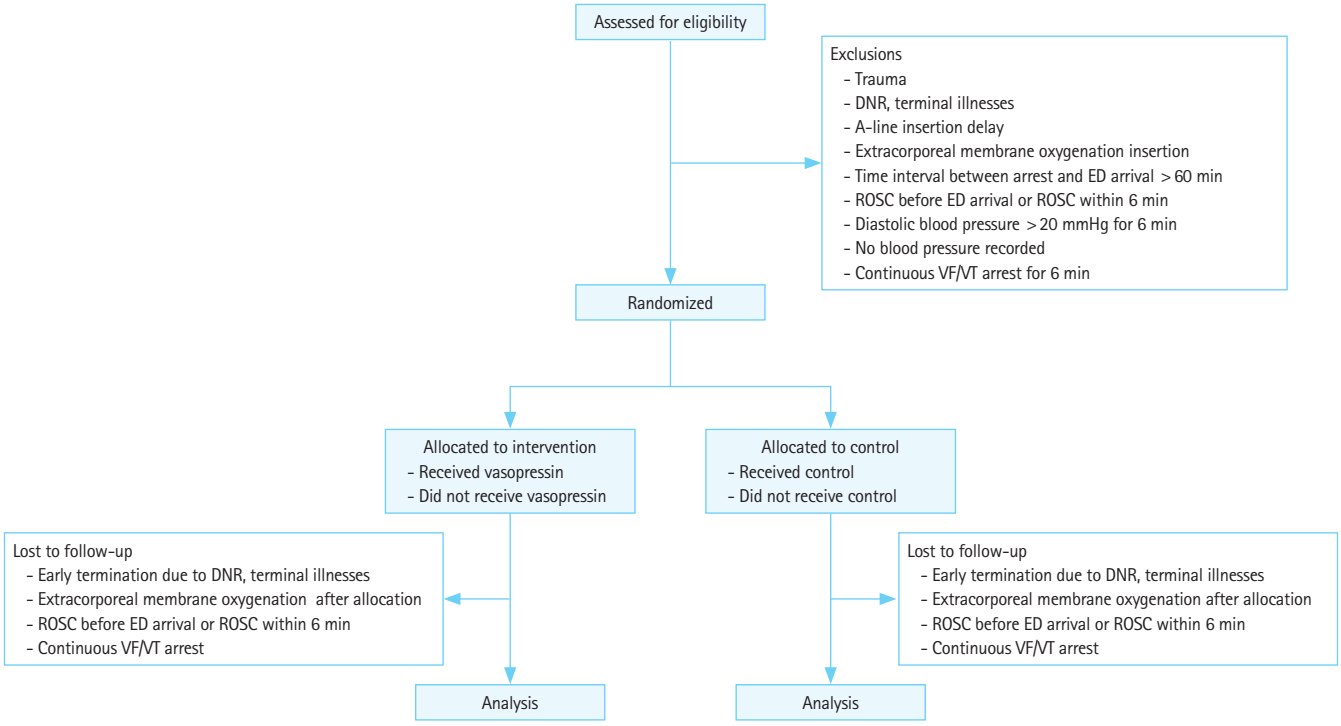

Fig. 1. Trial flowchart. DNR, do not resuscitate; ED, emergency department; ROSC, return of spontaneous circulation; VF, ventricular fibrillation; VT, ventricular tachycardia.

METHODS

Ethical statements

The trial protocol was approved by the Institutional Review Board of Asan Medical Center (No. 2017-0669) and the Ministry of Food and Drug Safety in Korea. The requirement for informed consent was waived by the Ethics Committee because of the emergent need for treatment in cardiac arrest. The legal representatives of the patients were later informed about the trial.

Study design

We will conduct a randomized, double-blind, placebo-controlled, single-center trial among patients with nontraumatic OHCA in the emergency department of an urban, tertiary hospital, located in Seoul, Korea. Figs. 1 and 2 show the study flow chart and the schedule, respectively. A SPIRIT (Standard Protocol Items: Recommendations for Clinical Interventional Trials) checklist is also available (Supplementary Material 1).

Eligibility criteria

Adult patients (above 18 years old) with nontraumatic, nonshockable OHCA and with diastolic blood pressure below 20 mmHg measured by invasive radial or femoral arterial line at presentation will be included. The following exclusion criteria apply: patients with traumatic cardiac arrest, patients with a signed do-not-resuscitate order, patients with an underlying terminal-state disease without an active treatment plan, patients with failed arterial line insertion within 6 minutes, patients receiving extracorporeal membrane oxygenation, patients with a prehospital downtime longer than 60 minutes, patients with successful ROSC before hospital arrival or ROSC within 6 minutes, and patients with diastolic blood pressure above 20 mmHg for 6 minutes during resuscitation.

Randomization and study medication

The patients will be randomly assigned in a 1:1 ratio via a random number generator to either the intervention group or the placebo

	Study period							
	Enrollment	Allocation	Post-allocation					Close-out
Time point (min)[a]	≤ 6 min	0	8	9	10	11	End[b]	Hospital results[a]
Enrollment								
Eligibility screen	X							
Arterial line insertion	X							
Monitoring continuous arterial diastolic blood pressure	←	—	—	—	—	—	→	
Allocation		X						
Intervention								
Vasopressin (40 IU with epinephrine 1 mg)			X		X			
Control (saline 40 mL with epinephrine 1 mg)			X		X			
Assessments								
Baseline characteristics according to Utstein guidelines	X	X						
Trends of end-tidal carbon dioxide levels and diastolic blood pressure	←	—	—	—	—	—	→	
Results of resuscitation							X	X

Fig. 2. Trial schedule. [a]Assessment of survival discharge, favorable neurologic outcome (Cerebral Performance Category 1 or 2). [b]Terminations of cardiopulmonary resuscitation were decided by emergency medicine physicians on duty after return of spontaneous circulation or declaration of death.

group. The trial administration nurse will open a premade, concealed, uniquely numbered, but otherwise identical-appearing card containing a treatment (i.e., vasopressin or placebo). Then, he/she will prepare the vasopressin (40 IU) or saline placebo. During the trial, all emergency physicians, nurses, and interns will be unaware of which drugs will be used. Unblinding will only take place in case of an unexpected serious adverse reaction. After randomization, patients will receive either 1 mg of epinephrine and 40 IU of vasopressin or 1 mg of epinephrine and saline placebo in separate injections less than 10 seconds apart. If ROSC is not achieved within the following 3 minutes, patients will be administered one more vasopressin (40 IU) or placebo with epinephrine injection. After that, only 1 mg of epinephrine will be administered every 3 minutes for both groups. Other conventional drugs, including amiodarone, calcium, or bicarbonate will also be administered at the clinician's discretion and no other drugs will be administered.

Clinical management

Advanced cardiac life support will be administered in accordance with the last international guidelines and local procedures.[5,6] In brief, all cardiac arrests presenting to the emergency department will have resuscitation initiated while being assessed for eligibility. Defibrillation will be performed for patients with shockable rhythms. In eligible patients, an arterial line will be placed for continuous monitoring via the radial or femoral arteries. Confirmation of adequate placement of the catheter will be performed by an experienced emergency physician on duty using bedside ultrasonography. Moreover, an arterial line square wave test will be conducted to confirm adequate function of invasive catheters. Survivors who are successfully resuscitated will be admitted to intensive care units for further postcardiac arrest care, including targeted temperature management, percutaneous coronary intervention, mechanical ventilation, and renal replacement therapy.

Data and laboratory measurements

All data will be anonymized and collected according to Utstein guidelines using a database designed with Microsoft Access (Microsoft Corp., Redmond, WA, USA) by independent blinded researchers.[18] Baseline characteristics and other laboratory variables will be obtained from electronic medical records at the study facility. We will also collect prehospital information, including prehospital total no-flow and low-flow time, presence of shockable rhythm, administration time of epinephrine, and amount of epinephrine. In addition, arterial blood pressure and end-tidal carbon dioxide levels during resuscitation will be recorded on video and recorded in the electronic database every 10 seconds. Arterial blood gases will be performed initially, at 10 minutes, at 20 minutes, and at the end of resuscitation. All case-record data will be subsequently collected in a database, where a random sample of 10% of the data will be assessed by the data and safety monitoring committee.

Outcome measures

The primary outcome will be sustained ROSC defined as the spontaneous return of a palpable pulse and measurable blood pressure longer than 20 minutes. Secondary outcomes are (1) survival to discharge, (2) good neurologic recovery at discharge (Cerebral Performance Category 1 or 2),[19] (3) elevation of diastolic blood pressure, (4) elevation of end-tidal carbon dioxide levels, and (5) improvement of acidosis and lactate levels. Diastolic blood pressure and end-tidal carbon dioxide levels will be obtained every 10 seconds from a recording of the entire resuscitation period. Then, trends and median values will be compared between groups. Acidosis and lactate levels will be obtained from arterial catheters on initial placement and 10 and 20 minutes later.

Adverse events

Risks to participants in this study may be minimal. There are no previous reports about harmful effects of administration of vasopressin up to 80 IU for patients with OHCA during resuscitation. Therefore, we have no predefined adverse events for this trial.

Statistical analysis

Data analysis will be performed with the intention-to-treat set, the full analysis set, and the per-protocol analysis set. The sample size was calculated based on an expected difference of 25%. We assumed that 30% of patients in the control group would achieve ROSC. For the P-value of 0.05 and the statistical power of 0.80, a total sample size of 74 patients will be required in each group. Assuming a 15% dropout rate, we will enroll 174 patients. All collected data will be analyzed using descriptive methods according to the intervention and control group. For continuous variables, mean with standard deviation or median with interquartile range will be presented depending on normality. For binary variables, number with percentage will be reported. Analysis will employ the t-test or the Mann-Whitney U-test for continuous variables and the chi-square test or Fisher exact test for categorical variables. Statistical significance will be considered as a P-value less than 0.05. All statistical analysis will be conducted using IBM SPSS ver. 27.0 (IBM Corp., Armonk, NY, USA).

DISCUSSION

Vasopressors have been considered key elements for improving chance of ROSC for patients with out-of-hospital cardiac arrest.

Despite vasopressin being more effective than epinephrine in animal studies, past meta-analysis of clinical studies showed no evident benefit of vasopressin over epinephrine in human CPR.[20,21] While the main focus of previous trials was universal administration of vasopressin during resuscitation, the key goal of this trial was to assess the effects of vasopressin on outcomes only among patients with cardiac arrest who cannot maintain diastolic blood pressure above 20 mmHg. Because vasopressin is another vasopressor which has a different mechanism from epinephrine, it may have a synergic effect with epinephrine for the patients in a severe vasoplegic state during CPR.[22]

The current guidelines suggest monitoring diastolic blood pressures and improving the quality of resuscitation when the level of diastolic blood pressures is lower than 20 mmHg.[5,6] Although insertion of an arterial line during chest compressions can be technically difficult, it is worth attempting not only for hemodynamic-directed CPR but also for monitoring dynamic changes in acid-base metabolism.[23,24] Accessing the radial or femoral artery with catheters will be attempted and adequate placement and function of the catheters will be confirmed by bedside sonography and square wave test. Failed insertion of the arterial line is an exclusion criterion, and withdrawal due to failed arterial line insertion may be higher than expected. However, at least two experienced emergency physicians on duty will try to insert the catheter to reduce exclusion of cases.

The patients will receive 40 IU of vasopressin just after administration of 1 mg epinephrine and receive one more repeated dose of both if ROSC is not achieved. This dosage of vasopressin has been proven to be safe without serious adverse outcomes in past clinical trials.[25] Furthermore, we will exclude patients with shockable rhythms (i.e., ventricular fibrillation and ventricular tachycardia) because in those cases immediate defibrillation is more important than arterial catheterization, which is a time-dependent procedure in this trial.

Enrollment of the patients started from August 2017. Along with a recent trial with in-hospital cardiac arrest patients, this study will provide valuable evidence about the effectiveness of the addition of vasopressin to epinephrine among patients with refractory low organ perfusion pressure in resuscitation of OHCA. If this treatment is shown to be effective, the use of an arterial line for monitoring diastolic blood pressure and administration of additional vasopressors could be a promising treatment strategy for patients with OHCA.

SUPPLEMENATARY MATERIAL

Supplementary Material 1. SPIRIT (Standard Protocol Items: Recommendations for Clinical Interventional Trials) checklist for trials. Supplementary material is available at https://doi.org/10.15441/ceem.22.367.

CONFLICT OF INTEREST

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

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AUTHOR CONTRIBUTIONS

Conceptualization: WYK, SMR; Data curation: JK, YJK; Formal analysis: DKO, JK; Funding acquisition: WYK; Investigation: SMK, SIH; Methodology: DKO, JK, BC; Project administration: WYK; Visualization: JK, YJK, SMR, SMK, SIH, BC; Writing–original draft: DKO, JK; Writing–review & writing: YJK, SMR, WYK.
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Commentary

Using the diastolic shock index to determine when to promptly administer vasopressors in patients with septic shock

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Fluid administration and vasopressor support are widely accepted first-line therapies intended to restore sepsis-induced tissue hypoperfusion. The former assumes that absolute or relative hypovolemia is always present during the early stages of septic shock, while vasopressor support is usually reserved for cases in which the initial fluid loading fails to correct hypotension or when arterial pressure is judged to be insufficient to restore tissue perfusion.[1] The cardiovascular dysfunction observed during septic shock results from complex interactions among hypovolemia, vasodilation, myocardial dysfunction, altered blood flow distribution, and endothelial and microcirculatory dysfunction.[2] In addition, imbalances among sympathetic, cholinergic, and anticholinergic inflows may affect inflammatory and immunologic responses beyond their direct effects on the heart and vessel walls. Therefore, different pathophysiological mechanisms determine the progression of circulatory failure, tissue hypoperfusion, and altered cell respiration and metabolism in patients with septic shock. These mechanisms evolve differently over time and vary from patient to patient as the septic shock progresses. Thus, while relative hypovolemia is thought to predominate in the very early phases of septic shock, most patients are not severely hypovolemic; conversely, their cardiovascular failure is widely marked by a loss of vascular tone. Even though these dissimilar mechanisms produce a common profile characterized by hypotension, tissue hypoperfusion, and elevated lactate levels, the management of septic shock should be based on a personalized approach that includes the following: administering fluids when hypovolemia predominates and fluid responsiveness is documented; adjusting vasopressor doses when it is judged that vasoplegia is the preponderant mechanism underlying hypotension, thus limiting unnecessary fluid administration; adding inodilators when myocardial dysfunction is recognized or when hypoperfusion persists despite appropriate fluid resuscitation and attaining adequate blood pressure levels; decreasing vasopressor or inodilator doses when dynamic left ventricular outflow tract obstruction is recognized; and individualizing the mean arterial pressure (MAP) according to levels established prior to the shock episode. In other words, an initial well-conducted resuscitation should be based on individualized signals of tissue hypoperfusion and macrohemodynamic derangements.

A decrease in vascular tone represents one of the leading mechanisms associated with hypotension and tissue hypoperfusion in septic shock,[3] and it is fundamentally characterized by a progressively impaired response from the vascular smooth muscle to endogenous circulating and

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exogenous vasoconstrictors. Classically, a low diastolic arterial pressure (DAP) has been recognized as an indirect sign of vasodilation, although the *in vivo* assessment of vascular tone (i.e., during dynamic conditions) is not standardized and has been classically based on indirect measurements of vascular resistances.[4] Under normal conditions, the DAP is mainly determined by vascular tone, and it remains nearly identical from the center to the periphery (i.e., from the ascending aorta to the peripheral vessels).[5] In contrast, the systolic arterial pressure (SAP) and consequently the MAP may greatly vary from the aorta to the peripheral vessels as long as peripheral arterial elastance varies. Thus, discrepancies in the SAP and MAP from the center to the periphery are expected during vasodilatory conditions, while DAP values remain virtually identical independently from the site in which they are assessed, even in the presence of severe vasodilation. Nevertheless, the operational definitions of different types of septic shock classically include the reduction of MAP and/or SAP, which acknowledges the pivotal role of both MAP and SAP on organ perfusion, in addition to the clinical prognostic value of sustained low MAP during the shock process. Even though the DAP is not considered when categorizing the severity of septic shock, an evaluation of the DAP could have significant clinical implications, especially when the underlying mechanism of shock is vasodilation (as occurs in septic shock).

If the aortic valve is competent, the DAP reflects (to some extent) the vascular tone. However, the DAP should not be evaluated separately from the heart rate (HR) because acute reductions in arterial pressure and vascular tone are compensated for by increases in sympathetic activity, which ultimately will affect the HR. Remarkably, the DAP is influenced by the duration of the cardiac cycle, the blood volume ejected into the aorta, and the overall arterial compliance.[6] Thus, under isovolemic conditions and constant arterial compliance, a shortening of diastolic times should result in a higher DAP, while prolonged diastolic times would lead to opposite effects.[6] Consequently, during pathological conditions, simultaneous and divergent variations in the DAP and HR (i.e., a progressively lower DAP combined with more severe tachycardia) should suggest more severe cardiovascular dysfunction, with shorter diastolic times unable to compensate for a DAP decrease as a consequence of the progressive loss of vascular tone. A recent study evaluated the relationships between HR:DAP ratios (i.e., the diastolic shock index [DSI]) recorded just before or at the start of vasopressor support and the clinical outcomes in patients with septic shock.[7] Three important findings were noted: (1) higher DSI values calculated just before or at the start of vasopressor administration were associated with a gradual increase in the risk of death in patients with septic shock; (2) isolated low DAP or high HR values did not clearly identify such a risk; and (3) nonsurvivors evolved with persistently high DSI values and required higher doses of vasopressors and more resuscitation fluids than survivors. In a similar way, a recent retrospective study showed that DSI and lactate values identified patients who were more likely to require a vasopressor in the context of hypotension and suspected infection.[8] Even though these results are in line with previous reports,[7] the usefulness of DSI in clinical practice has not yet been demonstrated.

A recent observational study suggested that the very early administration of vasopressors in septic shock might be associated with better clinical outcomes.[9] The patients subjected to very early vasopressor use in that cohort received a lower volume of resuscitation fluids, exhibited less net fluid accumulation, and had shorter hypotension times.[9] Similarly, in a recently published study, patients with simultaneous increases in their lactate and DSI levels had a lower 28-day mortality risk when vasopressors were initiated very early.[8] In contrast, others have reported opposite results when vasopressors were introduced very early during the resuscitation process,[10] although it is not clear that this difference indicated an effect of the early start of vasopressors or simply reflected the presence of a more severe disease condition. Regardless of whether the immediate introduction of vasopressors was advantageous, it also remains to be determined which patients would benefit the most from this strategy. Intuitively, more prominent beneficial effects of very early initiation of vasopressors should be observed in cases of more severe vasodilation. In line with this hypothesis, septic patients with higher prevasopressor DSI values had significantly better clinical outcomes when vasopressors were administered early, while such an effect was not evident in those with lower DSI values.[7]

In conclusion, even though hypotension and hyperlactatemia are recognized markers of septic shock, resuscitative interventions should be tailored to each individual because different mechanisms are involved in sepsis-related cardiovascular dysfunction. As there are no unequivocal signals that indicate when vasopressor support should be initiated in hypotensive patients with a suspected infection, surrogates of severe vasodilation should suggest its immediate requirement; therefore, DSI could be a useful tool for this purpose and should be tested in future clinical trials.

CONFLICT OF INTEREST

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Case Report

A case report of ivory vertebra sign: an initial radiological manifestation of underlying abdominal malignancy

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Low back pain is one of the most common presenting complaints in the emergency department, and a plain radiograph of the lumbar spine is usually the first diagnostic modality. The ivory vertebra sign refers to the radiological appearance of a smooth, white ivory-like appearance of the affected single vertebra or multiple vertebral bodies. It is sometimes the initial radiologic manifestation of a variety of infectious, neoplastic, or metabolic diseases. Subsequent computerized tomography and magnetic resonance imaging are generally indicated to characterize the details, as well as look for other occult lesions. It is therefore important for emergency physicians to be aware of this, as this will aid in the appropriate evaluation and rapid diagnosis of the underlying disorder.

Keywords Back pain; Ivory vertebra; Carcinoma; Neoplasm metastasis; Case reports

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Capsule Summary

What is already known

Ivory spine is a rare sign that refers to the radiological appearance of the affected vertebra, which looks smooth, white, and ivory-like.

What is new in the current study

Ivory spine on a plain lumbar radiograph is sometimes the only initial radiologic manifestation for a variety of underlying infective, neoplastic or metabolic diseases. It is therefore important for the emergency physicians to be aware of this, as prompt further evaluation with advanced imaging is required to diagnose the underlying condition.

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INTRODUCTION

Low back pain is one of the most common presenting complaints for underlying spinal pathology, and a plain radiograph of the lumbar spine is usually the first diagnostic imaging modality. The "ivory vertebra" sign refers to the radiological appearance of the affected vertebra that looks smooth, white, and ivory-like; however, this is clinically rare. We present a rare case of a female patient who presented to the emergency department with complaints of lower back and was diagnosed with ivory vertebra on plain lumbar spine radiography, leading to further evaluation.

CASE REPORT

A 77-year-old female patient presented to the emergency department with low back pain that had been increasing in intensity over the past 2 weeks. She also complained of occasional lower abdominal pain and feeling bloated. She denied any complaints of fever, weight loss, loss of appetite, or change in bowel habits. She was seen by a general practitioner, who treated her for gastritis with symptomatic medications; however, her symptoms persisted. She had been feeling lethargic over the last 3 days. She had a past medical history of diabetes, hyperlipidemia, ischemic heart disease, hyperthyroidism, and left middle cerebral artery stroke with good functional recovery. She was compliant with her daily medications.

On examination, her vital signs were as follows: heart rate, 117 beats/min; respiratory rate, 17 breaths/min; and blood pressure, 124/82 mmHg. Her abdominal examination was normal. There was no spinal tenderness, and her bedside ultrasound was normal. Blood test results showed a hemoglobin level of 9.4 g/dL and potassium concentration of 3.1 mmol/L. The remaining electrolytes, amylase, and renal panel were normal. Urine examination showed leucocytes. Chest X-ray showed a few nodular densities over the right retrocardiac region and a calcific density over the subcarinal region, representing a calcified lymph node. Anteroposterior (Fig. 1A) and lateral (Fig. 1B) views of the lumbar spinal X-ray showed a diffuse increase in radiodensity and sclerosis of the L2 and L3 vertebral bodies. Computed tomography of the abdomen and pelvis showed short-segment irregular annular mass-like thickening involving the lower sigmoid colon, suspicious for

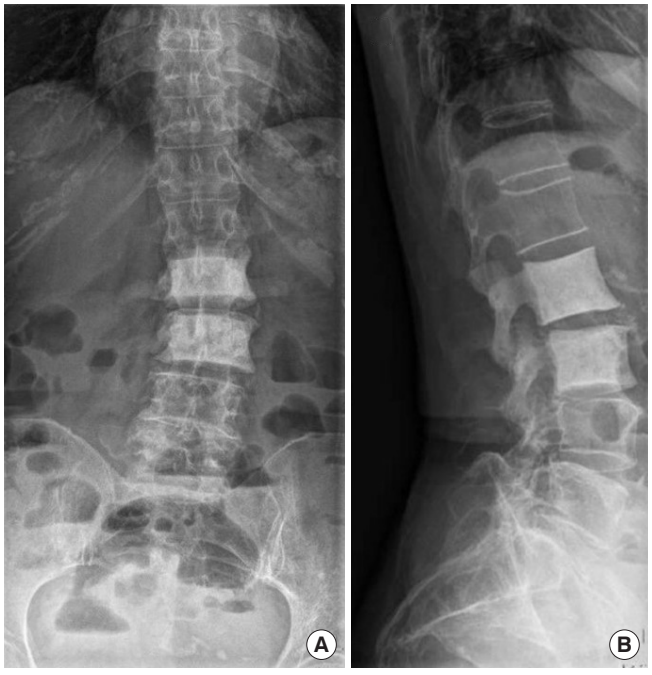

Fig. 1. X-ray of (A) anteroposterior and (B) lateral views of the lumbar spine showing diffuse sclerosis in the body of L2 and L3 vertebrae, known as "ivory vertebra."

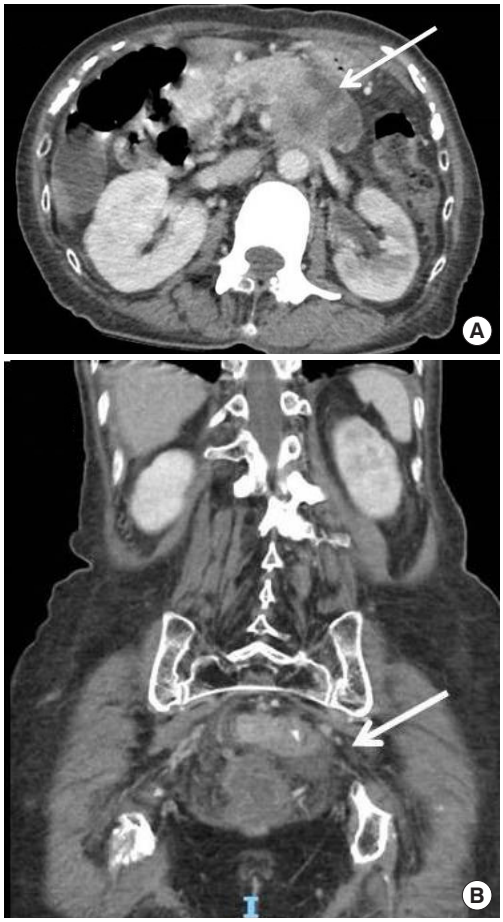

Fig. 2. Computed tomography scan of abdomen and pelvis showing (A) heterogeneous mass-like enlargement of the distal pancreatic body, suspicious for primary pancreatic malignancy with necrotic change (arrow), and (B) annular mass-like thickening involving the lower sigmoid colon, suggestive of primary colonic malignancy (arrow).

primary colonic malignancy (Fig. 2A), and a heterogeneous mass-like enlargement of the distal pancreatic body with cyst-like hypodensities within, suspicious for either a primary pancreatic malignancy (i.e., adenocarcinoma) with necrotic change or a malignant cystic neoplasm (Fig. 2B). There were associated sclerotic metastases of the L2 and L3 vertebrae. Her CA 19-9 and carcinoembryonic antigen levels were elevated. She was, thus, diagnosed with synchronous pancreatic and rectal malignancy with bony metastases and admitted to the hepatobiliary department for further management. Then, following a discussion of the case at a tumor board meeting, palliative chemotherapy was initiated. The patient, unfortunately, died after 3 months during follow-up. Tha patient's next of kin provided written informed consent for publication of the research details and clinical images.

DISCUSSION

The vertebral body is normally composed of vascularized trabecular bone, also known as spongy bone. In the ivory vertebra, this trabecular pattern is replaced by homogenous opacification due to the activation of osteoblasts by the underlying disease.[1] This uniform and diffuse sclerosis of the vertebral body gives it a hyperdense appearance. The vertebral body otherwise retains its size and shape, and sclerosis does not involve the adjacent intervertebral discs.[2,3] This increased opacity may either involve a single vertebra or multiple vertebral bodies. In general, a diffuse increase in vertebral bony density is referred to as ivory vertebra, but there are specific imaging characteristics that can point towards an underlying diagnosis. For example, in blastic metastases, the stimulation of osteoblasts leads to irregular replacement of the spinal trabecular bone by amorphous and dense bone masses. The diagnostic characteristics of metastases on imaging are seen as increased vertebral density, multiple spinal level involvement, and blastic lesions in posterior spinal elements.

When radiographs taken to investigate back pain show an ivory vertebra, further evaluation should be performed to look for the underlying causes, the commonest being osteoblastic metastatic carcinoma of the prostate and breast and Hodgkin's lymphoma.[1] In the elderly, it may also represent metastasis of pancreas and colon cancer, as in our case. It is also seen in Paget's disease, hemangioma, osteomyelitis, primary osteosarcoma, other skeletal metastasis, sarcoidosis, Pott's disease, and systemic mastocytosis.[4] It has also been noted in rare diseases like SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) syndrome and POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, skin lesions) syndrome.[5,6]

Plain radiographs of the spine and computed tomography scan will show diffuse, homogenous sclerosis of the vertebral body, which looks like ivory, with a variable degree of involvement of the posterior vertebral elements. Magnetic resonance imaging is generally indicated to characterize the details as well as to search for other occult lesions. On magnetic resonance imaging, hypointense, homogenously dark signals of the involved vertebra are seen on both T1- and T2-weighted images, and the intensity is directly proportional to the degree of sclerosis of the vertebral body.[2] Following this, a bone scan can be performed to identify lesions at other sites.

Ivory vertebra is sometimes the initial radiologic manifestation in a variety of infectious, neoplastic, or metabolic diseases. It is, therefore, important for emergency physicians to be aware of this as this will aid in the appropriate evaluation and rapid diagnosis of the underlying disorder.

CONFLICT OF INTEREST

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

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Clinical and Experimental Emergency Medicine

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Case Report

Fatal arrhythmia following ingestion of hawthorn root (*Crataegus pubescens*) extract: a case report

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The use of extracts from the hawthorn plant as cardiovascular agents dates back to the 1st century; recently, they have also been made available online as weight loss aids. Herein, we present a case of intentional intoxication with hawthorn root extract (HRE) in an adult patient that resulted in death. A 20-year-old female patient, who was clinically diagnosed with depression, developed hypotension, bradycardia, and depressed consciousness after ingestion of this extract. An electrocardiogram recorded a sinus arrest with a slow nodal rhythm, which rapidly deteriorated, leading to cardiac arrest. This case report illustrates the potentially fatal consequences of HRE for which the constituents have not yet been characterized. All physicians, especially those in the emergency department, should be aware of the dangerous, even potentially fatal interactions of HRE with prescription medications.

Keywords Long QT syndrome; Cardiac arrhythmias; Emergency medicine; Sudden cardiac death; Case reports

Capsule Summary

What is already known

Few herbal medications can have dangerous and even fatal interactions leading to arrhythmia and death.

What is new in the current study

Acute intoxication with hawthorn root extract in an adult patient resulted in arrhythmia and subsequent death.

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INTRODUCTION

The use of extracts from the hawthorn plant as cardiovascular agents dates back to the first century and is prevalent even today. Among its cardiovascular effects, hawthorn extracts demonstrate positive inotropic, vasodilatory, and antiarrhythmic effects.[1] Recently, preparations from hawthorn roots have been made available online as weight loss aids.[2] This report depicts a case of intentional intoxication with hawthorn root extract (HRE) in an adult patient that resulted in severe arrhythmia and subsequent death.

CASE REPORT

A 20-year-old female patient arrived at the emergency department (ED) complaining of abdominal pain and nausea. The patient did not have any history of chronic/neurodegenerative disease. Nevertheless, at admission, she was undergoing treatment for depression with amitriptyline, alprazolam, and clozapine. The patient had ingested all three medications simultaneously at 9:00 PM, the previous night (12 hours before admission).

She also reportedly ingested two alcoholic drink equivalents (consisting of 24 oz of regular beer) between 10:00 PM and 1:00 AM, on the day of admission. On further interrogation, the patient confessed to having ingested an undetermined number of HRE pills. The bottle was stated to contain 90 pills when sealed and was empty when brought to the ED by the patient's relatives, who estimated that the patient must have ingested over half the tablets in the bottle. Upon examination, the patient was responsive and oriented, with a Glasgow Coma Scale score of 15 points. Vital signs were normal. Routine lab work, including hemogram, renal function, and liver enzymes, were normal. Serum electrolytes were sodium, 142 mEq/L; potassium, 3.8 mEq/L; chloride, 111 mEq/L; magnesium, 2.0 mEq/L. The attending physician advised a gastric lavage (per protocol), and prescribed omeprazole 20 mg intravenous (IV), and ondansetron 4 mg IV.

After 6 hours in the ED, the patient abruptly became pale, and developed diaphoresis and nausea. Vital signs showed a blood pressure (BP) of 70/40 mmHg with pulse rate 30 beats per min (bpm), respiratory rate 20 breaths/min, and O_2 saturation 97% on room air. An electrocardiogram (ECG) was obtained (Fig. 1). The patient then received a 500 mL crystalloid fluid bolus and 1 mg atropine IV. Consequently, the pulse rate and BP improved to 80 bpm and 100/60 mmHg, respectively. The patient's vital signs stabilized, and she also reported symptomatic relief. The ECG showed sinus rhythm with sporadic premature ventricular contractions.

Nevertheless, after 15 minutes, there was a sudden drop in BP and pulse rate to 61/28 mmHg and 30 bpm, respectively. The patient was administered another 250 mL of crystalloid fluid bolus. Fig. 2 shows the ECG findings at this point. However, the patient was unresponsive to fluid resuscitation due to persisting hypotension and bradycardia, and was consequently shifted to the intensive care unit. There, she developed depressed consciousness

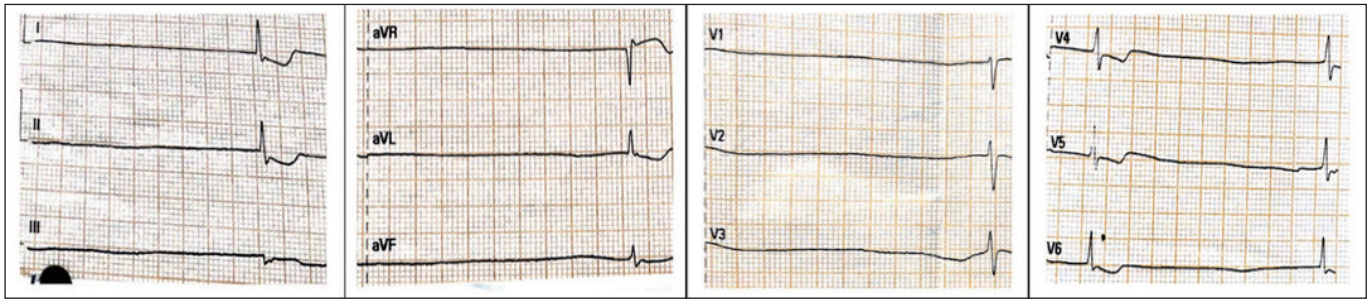

Fig. 1. Initial electrocardiogram showing sinus arrest with slow nodal rhythm and secondary changes of the ST segment and T wave.

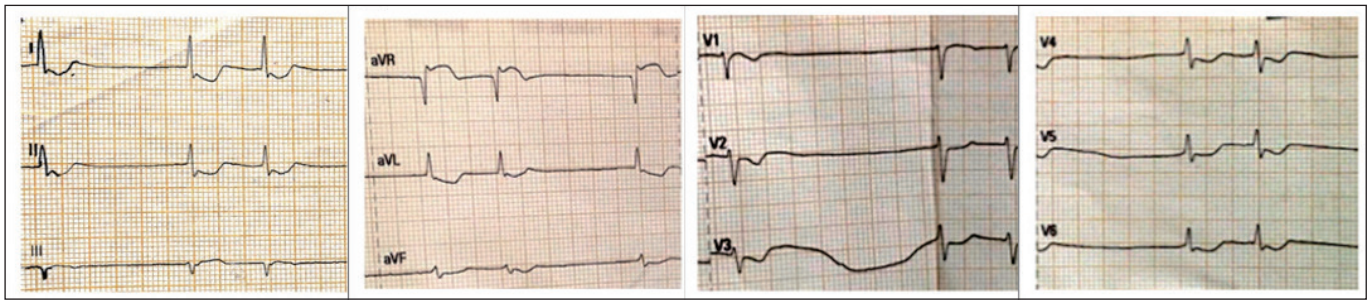

Fig. 2. Second electrocardiogram showing sinus arrest with nodal rhythm and secondary changes of the ST segment and T wave.

(Glasgow Coma Scale 13 points, E3 M6 V4). A solution containing 400 mg of dopamine in 250 mL of 5% dextrose, was initially administered at a rate of 5 μg/kg/min and then increased gradually up to 20 μg/kg/min; this led to improvements in pulse rate and BP to 60 bpm and 89/55 mmHg, respectively.

Approximately 40 minutes after her arrival to the intensive care unit, the patient went into a witnessed cardiac arrest. Cardiopulmonary resuscitation was started. The ECG showed ventricular fibrillation. Defibrillation restored rhythm to sinus bradycardia. After a minute passed, the patient sustained a new episode of cardiac arrest. The patient was unresponsive to advanced cardiovascular life support protocols, including lidocaine administration, and was pronounced dead after 20 minutes of effort.

DISCUSSION

This case depicts an extreme consequence of the use of HRE. A plausible mechanism for the fatal arrhythmia in this patient could be a ventricular arrhythmia caused by excessive QT prolongation from an overdose of HRE and its interaction with other medications; consequently, leading to a delay in the cardiac rectifier current (IKr).

Phytochemical analysis shows that epicatechin, aglycons, and glycosides of B-type oligomeric procyanidins, flavanols, phenolic acids, and C-glycosyl flavones are the major bioactive compounds in hawthorn (*Crataegus* spp.). The beneficial effects of these compounds on the cardiovascular system have been demonstrated through *in vitro*, animal, and clinical studies.[3]

Nevertheless, the adverse events associated with the ingestion of hawthorn extracts are less well known. In a systematic review of 14 trials evaluating hawthorn extract for treating chronic heart failure, 13 trials contained no data on relevant mortality and morbidity, such as cardiac events. Only one trial reported five deaths (three in the active group), but did not provide any details.[4] Another trial with 897 patients, who were treated with HRE, reported the occurrence of cardiac disorders at a frequency of 30% as a side effect. Nonetheless, the authors did not define the cardiac conditions, nor did the report provide further details on the nature of the side effects.[5] Additionally, flowers and leaves are the main components of most hawthorn extracts, with few utilizing the fruits,[6] and reports on the use of the roots are rare.[2]

The inhibition of IKr is a known effect of hawthorn,[1] and this inhibition antecedes the development of torsade de pointes, just as in the congenital long QT syndromes.[7] Although the patient had no history of long QT syndrome, the female sex and the presence of subclinical forms of long QT syndrome mutations are recognized risk factors for drug-induced torsade de pointes.[8]

Regarding drug-related QT interval prolongation, both amitriptyline and clozapine (which the patient regularly took without reporting adverse effects) have QT-prolonging capabilities.[9] These two mechanisms, acting either alone or in combination, could have led to the development of the patient's and subsequent death. Besides, both omeprazole and ondansetron are also reported to prolong the QT interval.[10] Multiple pharmacological targets of hawthorn extracts have been documented.[5] It is worth noting that the patient was under long-term psychiatric treatment with the drugs mentioned above, with good adherence and without reporting any adverse event. It is possible that the patient perceived HRE as safe (due to its so-called "natural" origin), and therefore, decided not to commit a suicidal attempt but only a suicidal gesture. This could provide a possible explanation as to why she did not overdose on her other available medications.

Thus, this might be a cautionary note to physicians regarding their drug choices for patients taking Mexican hawthorn root and other *Crataegus* spp. In a recent report, the ingestion of HRE in a pediatric patient resulted in clinical manifestations of digoxin intoxication with a false elevation of digoxin serum levels.[2] Clinical trials show that HRE intake is associated with a positive inotropic effect with an increase in ejection fraction of patients with heart failure.[5] Consequently, a digoxin-like effect of hawthorn may have also aggravated the arrhythmogenesis. Unfortunately, we could not obtain any measurement of the serum HRE and digoxin levels, which might have helped in establishing the causal relationship in our case.

Lastly, although the change in plasma sodium and potassium after gastric lavage was not considerable,[11] electrolyte disturbances have been documented, which could have further exacerbated the arrhythmogenesis.

In conclusion, this case illustrates the potentially fatal consequences of HRE. We believe that all physicians, especially those in the ED, should be aware of the dangerous, even possibly fatal, interactions of HRE with prescription medications.

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: JALM, JMMR; For-

mal analysis: all authors; Visualization: JALM, JMMR; Writing–original draft: JMMR; Writing–review & editing: all authors.
All authors read and approved the final manuscript.

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Clinical and Experimental Emergency Medicine

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Images in Emergency Medicine

Transcatheter arterial embolization in a haemorrhagic renal cyst with "rising tide sign"

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A 69-year-old male patient presented to our emergency department with sudden left-sided flank pain associated with macroscopic haematuria. There was no history of trauma. Haemoglobin was 11.4 g/dL and abdominal multidetector computed tomography demonstrated a left simple renal cyst with a thin line of blood collection (Fig. 1A). At 48 hours, a second episode of massive macroscopic haematuria occurred. Haemoglobin has dropped to 9.3 g/dL and multidetector computed tomography demonstrated an increased level of blood collection into the left renal cyst (Fig. 1B). The patient underwent selective (Fig. 2A) and superselective (Fig. 2B) left renal artery angiography that showed two microspots of blood extravasation. Endovascular embolization was performed. Final angiographic control demonstrated occlusion of bleeding extravasation (Fig. 2C). At 12 hours, macroscopic haematuria had resolved and haemoglobin data showed an upward trend to 11.0 g/dL. Imaging follow-up at 72 hours (Fig. 3A) and 1 month (Fig. 3B) demonstrated left renal cyst reduction in size.

Simple renal cysts are benign and usually asymptomatic, so no treatment is required. When they are symptomatic, as with haemorrhage, treatment might be necessary.[1] Only three cases of transcatheter arterial embolization of symptomatic patients with haemorrhagic renal cysts are described in the literature.[2,3]

As demonstrated by our clinical case, transcatheter arterial embolization of renal intracystic active bleeding as definitive treatment (like other body regions) may have advantages over surgery of a less invasive procedure, the possibility to progress from diagnosis to treatment in the same session, and the possibility of minor loss of normal renal parenchyma.[2-4] The patient pro-

Capsule Summary

What is already known

Symptomatic haemorrhagic renal cysts with macroscopic haematuria are usually treated by surgery.

What is new in the current study

We present a case of renal cyst with increased bleeding and "rising tide sign" on imaging that was treated by superselective arterial embolization with clinical resolution.

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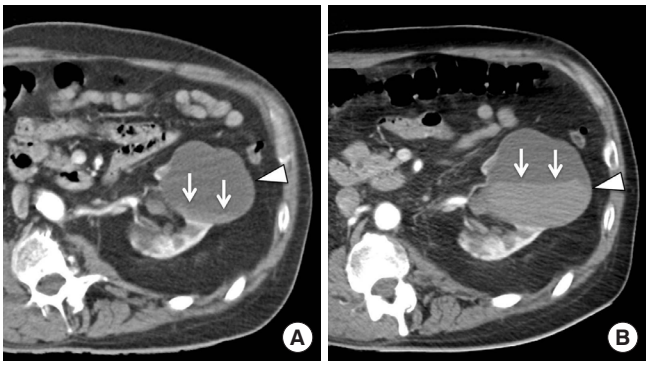

Fig. 1. Contrast-enhanced multidetector computed tomography axial image (A) showing a left simple renal cyst (arrowhead), hyperdense thin line of blood collection (arrows), and a volume of 165.7 mL, and (B) at 48 hours demonstrating a well-delineated left simple renal cyst (arrowhead) and increased level of hyperdense blood collection (imaging sign called "rising tide"; arrows) with a total volume of 347.6 mL.

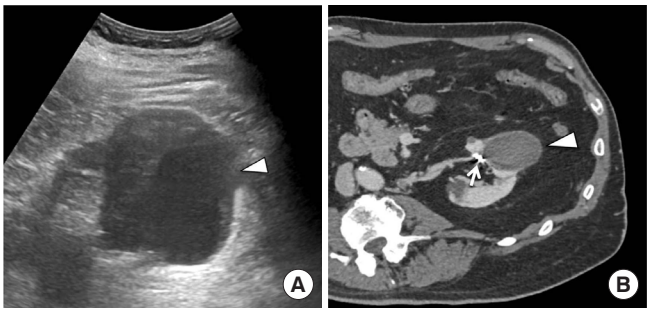

Fig. 3. (A) Left renal ultrasound control at 3 days confirming the presence of the left simple renal cyst (arrowhead) with initial reduction in size. (B) Contrast-enhanced multidetector computed tomography axial image at 1-month follow-up demonstrating significant reduction in size of the left simple renal cyst (arrowhead) to a volume of 67.8 mL. Note the metallic artefact of the deployed coil (arrow) into the embolized intraparenchymal branch of the left renal artery.

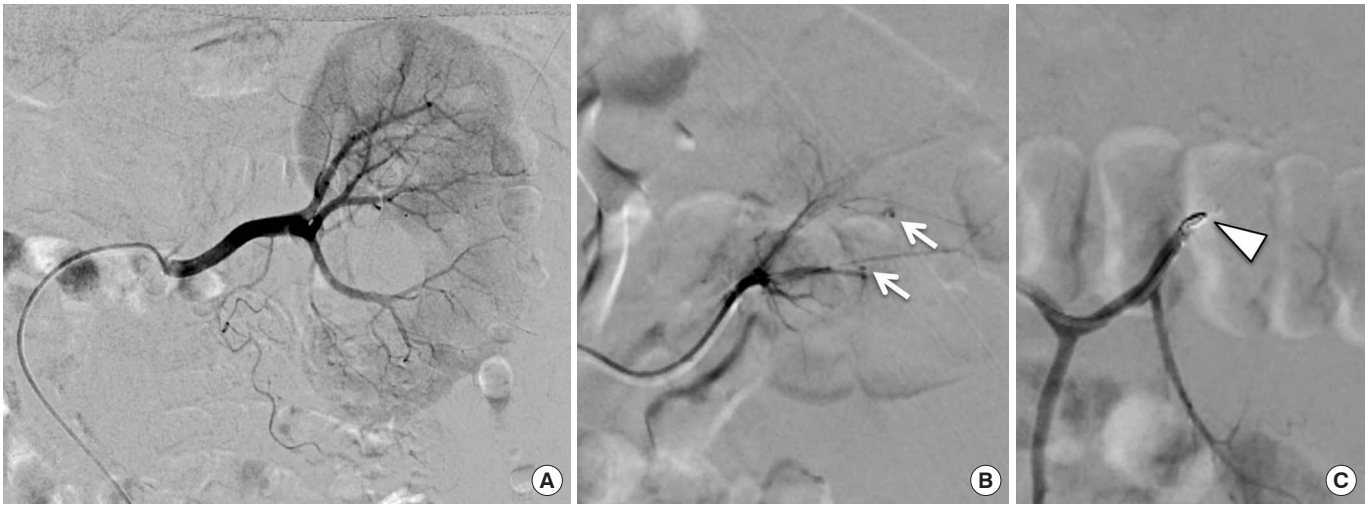

Fig. 2. (A) Selective left renal artery angiography and (B) superselective intraparenchymal angiography demonstrating the presence of two focal microspots of extravasation due to bleeding (arrows) at the middle third of the kidney. (C) Postembolization superselective intraparenchymal left renal angiography control showing a metallic artefact of the deployed coil (arrowhead) and occlusion of the two pathological arterial branches.

vided written informed consent for publication of the research details and clinical images.

CONFLICT OF INTEREST

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

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AUTHOR CONTRIBUTIONS

Conceptualization: UGR; Data curation: UGR, ML; Formal analysis: FN, FC; Visualization: UGR; Writing–original draft: UGR, FN; Writing–review & editing: UGR, FC, ML.
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Clinical and Experimental Emergency Medicine

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Images in Emergency Medicine

Unusual appearance of air in soft tissue on ultrasound

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A 46-year-old male patient with diabetes mellitus and prior right below-knee amputation presented with right thigh swelling and right knee pain for 3 days. Vital signs were temperature of 37.6°C, pulse rate of 96 beats/min, and blood pressure of 131/72 mmHg. His white blood cell count was 19,000/μL, and procalcitonin level was 8.05 μg/L. Bedside ultrasound of his amputation stump showed diffuse ring-down artifacts within an air-fluid collection (Fig. 1 and Supplementary Videos 1, 2), and X-rays of his right knee showed soft tissue gas (Figs. 2, 3). Magnetic resonance imaging showed subcutaneous air-fluid collection, knee effusion, myositis, and cellulitis without necrotizing fasciitis (Fig. 4). *Arcanobacterium haemolyticum* grew in aspiration sample of his knee. He underwent a right above-knee amputation 6 days after presentation. The patient provided written informed consent for publication of the research details and clinical images.

Gas in soft tissue is abnormal and should prompt the clinician to suspect an infection with gas-forming organisms when there is no trauma. In soft tissues, air commonly appears as echogenic foci with or without shadowing (depending on the amount of air). Air can appear as ring-down artifacts when there are multiple reflections of the ultrasound waves within a tetrahedron of air bubbles.[1] Numerous ring-down artifacts seen on soft tissue ultrasound of the present patient are likely due to a significant amount of air being present in a large fluid collection, resulting in large numbers of bubble tetrahedrons. Clinicians should be aware of this unusual appearance of air in a subcutaneous fluid collection, mimicking the interstitial syndrome on lung ultrasound.

Capsule Summary

What is already known

On soft tissue ultrasound, air commonly appears as echogenic foci with shadowing.

What is new in the current study

Air within soft tissue can appear as multiple diffuse ring-down artifacts on ultrasound, mimicking the appearance of interstitial syndrome on lung ultrasound.

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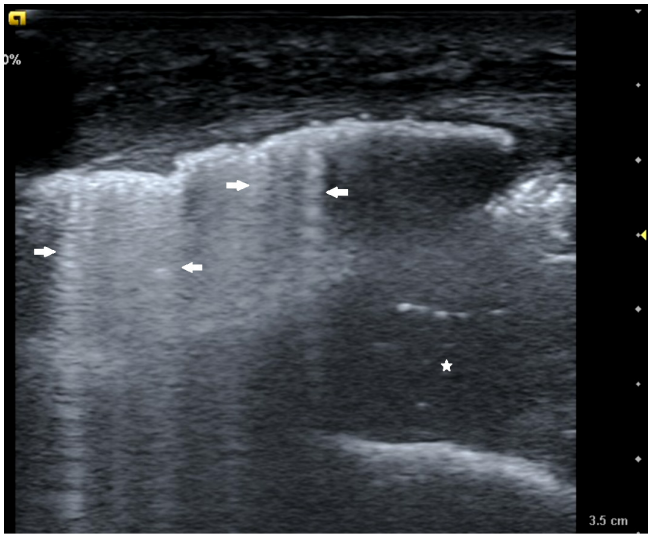

Fig. 1. Bedside ultrasound showing multiple ring-down artifacts (arrows) signifying gas in a fluid collection (star).

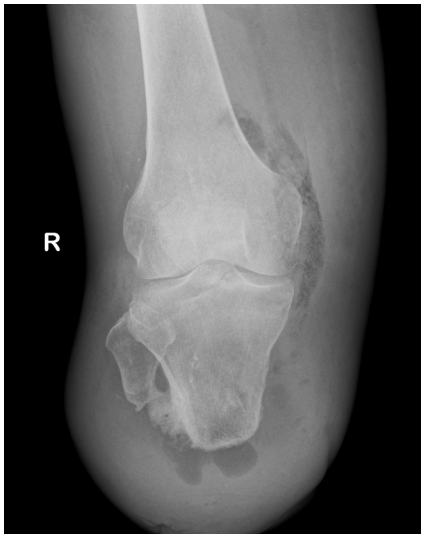

Fig. 2. Anteroposterior view of knee radiograph showing soft tissue gas.

SUPPLEMENTARY MATERIAL

Supplementary Video 1. Bedside ultrasound showing multiple ring-down artifacts from gas in a subcutaneous fluid collection, mimicking interstitial syndrome on lung ultrasound. Written informed consent for publication of the video was obtained from the patient.

Supplementary Video 2. Fluid within a collection can be seen in motion on probe compression. Written informed consent for publication of the video was obtained from the patient.

Supplementary materials are available at https://doi.org/10.15441/ceem.22.219.

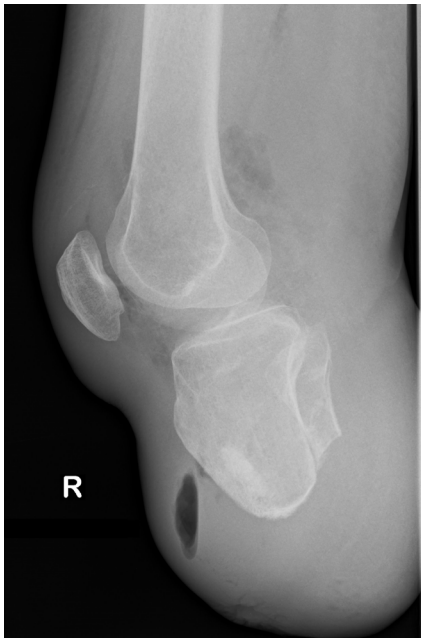

Fig. 3. Lateral view of knee radiograph showing soft tissue gas and a fluid collection with an air-fluid level.

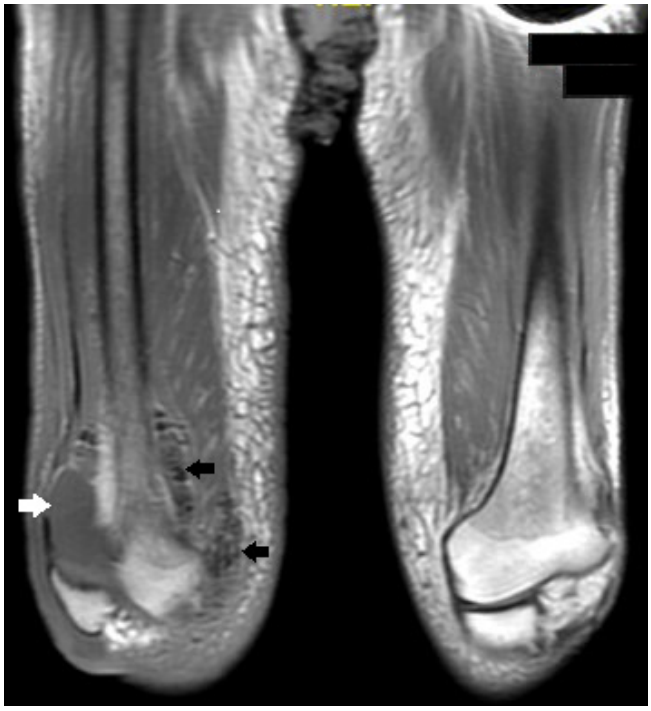

Fig. 4. Magnetic resonance imaging showing joint effusion (white arrow) and soft tissue gas (black arrows).

CONFLICT OF INTEREST

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

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Dispatcher-assisted first aid in chest pain: proposal of an evidence-based algorithm

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Dear Editor,

Chest pain is one of the most common reasons to seek emergency care, and 12% to 20% of persons who present to an emergency department with chest pain are ultimately diagnosed with acute coronary syndrome (ACS)[1]—a major cause of death worldwide. Although increased time from symptom onset to treatment is strongly associated with increased mortality from ACS, most individuals with chest pain do not receive timely aid, potentially leading to poor outcomes.[2]

Along with mass public awareness and education campaigns aiming at promoting early recognition of chest pain as a threatening sign of ACS and rapid activation of emergency medical services (EMS), broad implementation of practice where EMS dispatchers provide pre-arrival instructions (PAI) on first aid over the telephone may contribute to a reduction in delay to treatment in ACS. Nevertheless, this subject has received scant attention in the research literature,[3] and no unified evidence-based approach to dispatcher assistance in chest pain exists to date.

As a first step toward development of a standardized algorithm for dispatcher assistance in chest pain, in July 2022, a comparative analysis of recommendations on first aid in chest pain from English-language guidelines was carried out. The analysis revealed disagreement between the guidelines (see dataset[4]). In particular, a number of guidelines, including those published since 2020, lack recommendations to limit physical activity of the person who suffers chest pain, assist them to take prescribed antianginal medication, monitor responsiveness and breathing to arrival of an ambulance, and immediately start cardiopulmonary resuscitation if the person becomes unresponsive and stops breathing normally. Some guidelines do not explicitly recommend prompt EMS for persons with acute chest pain, and most guidelines do not emphasize that transportation of such individuals to a healthcare facility should not be performed via private vehicle. All but one guideline encourage adults with nontraumatic chest pain to take aspirin while awaiting EMS, unless contraindications exist.

Additional analysis was conducted to investigate content of dispatch PAI on first aid in chest pain. Five sets of English-language PAI were found through Google search, all developed in the US, dated from 2008 to 2022 (see dataset[4]). Of these, four sets do not include the instruction to stop physical activity of the person with chest pain; four sets and one set do not encourage the person to take aspirin or prescribed antianginal drug, respectively; and three sets contain a nonevidence-based instruction to loosen the person's tight clothing. Absence of simple and well-justified recommendations on first aid from PAI, as well as inclusion of nonevidence-based instructions, could lead to suboptimal care of ACS and impair outcomes of this time-sensitive emergency.

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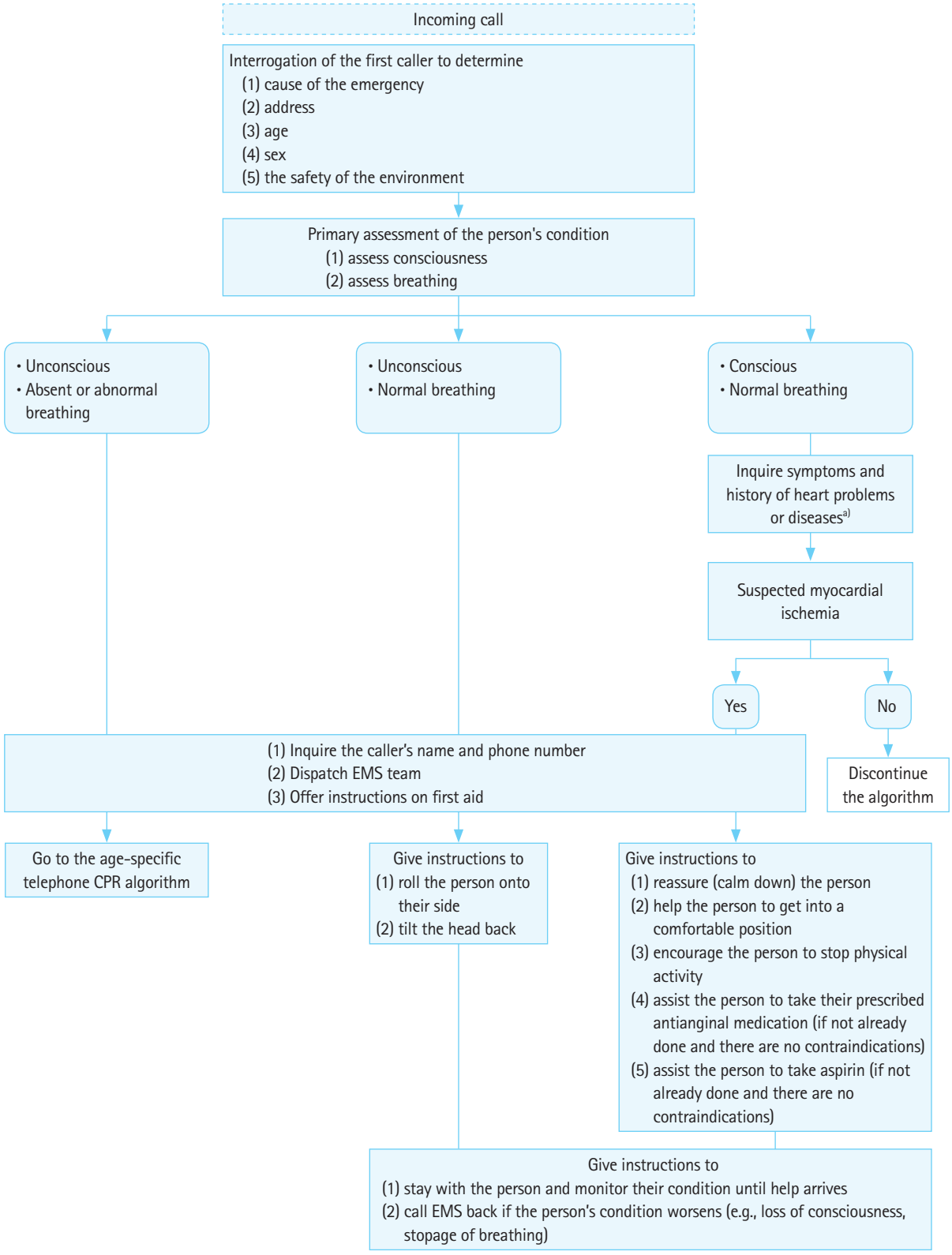

Fig. 1. Algorithm for telephone dispatcher assistance in chest pain. CPR, cardiopulmonary resuscitation; EMS, emergency medical services. [a)]If the person is responsive, the dispatcher should inquire about symptoms of possible acute coronary syndrome, including pain location and duration; changes of the pain when moving or breathing; and combination of the chest pain with profuse sweating, nausea, vomiting, weakness, dizziness, dyspnea, syncope, confusion, or rapid heart rate.

Based on the analysis and considering related work,[5] an algorithm of telephone dispatcher assistance in chest pain was designed and is proposed for scientific discussion and further experimental and clinical evaluation (Fig. 1). Founded on the guidelines' integrated evidence, the algorithm could contribute to creation of a standardized framework for large-scale implementation of dispatcher-assisted first aid in chest pain.

CONFLICT OF INTEREST

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

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Erratum

Erratum to "Validation and modification of HEART score components for patients with chest pain in the emergency department"

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In the article entitled "Validation and modification of HEART score components for patients with chest pain in the emergency department,"[1] the data collection period for MACE incidence was incorrectly stated as "MACE incidence within the previous 3 months" in the "Data collection" section under METHODS. It has been corrected to "MACE incidence within 3 months."

Before correction

Data on patients' baseline characteristics (sex, age, smoking, familial history of coronary artery disease [CAD], aspirin use in the past 7 days), underlying disease (hypertension, diabetes mellitus, obesity, dyslipidemia, atherosclerotic disease), initial vital signs (systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate), history, initial troponin-I level, ECG results, HEART score, and **MACE incidence within the previous 3 months** were obtained and evaluated retrospectively.

After correction

Data on patients' baseline characteristics (sex, age, smoking, familial history of coronary artery disease [CAD], aspirin use in the past 7 days), underlying disease (hypertension, diabetes mellitus, obesity, dyslipidemia, atherosclerotic disease), initial vital signs (systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate), history, initial troponin-I level, ECG results, HEART score, and **MACE incidence within 3 months** were obtained and evaluated retrospectively.

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