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# Journal of Neurocritical Care

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## Aims and Scope

Journal of Neurocritical Care (JNC) aims to improve the quality of diagnoses and management of neurocritically ill patients by sharing practical knowledge and professional experience with our reader. Although JNC publishes papers on a variety of neurological disorders, it focuses on cerebrovascular diseases, epileptic seizures and status epilepticus, infectious and inflammatory diseases of the nervous system, neuromuscular diseases, and neurotrauma. We are also interested in research on neurological manifestations of general medical illnesses as well as general critical care of neurological diseases.

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# Editorial Board

Journal of Neurocritical Care

# Contents

Journal of Neurocritical Care

Vol. 15, No. 1, June 2022

## REVIEW ARTICLE



## ORIGINAL ARTICLE



## CASE REPORT



## IMAGES IN NEUROCRITICAL CARE

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Journal of Neurocritical Care

# Gut microbiome and neurocritically ill patients

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REVIEW ARTICLE

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Since the times of Rokitansky and Cushing, we have been fascinated by the connections between the gut and the brain. Recent advances in next-generation sequencing techniques have shown that this relationship is even more complex and integral to our sense of self than previously imagined. As these techniques refine our understanding of the abundance and diversity of the gut bacterial microbiome, the relationship between the gut and the brain has been redefined. Now, this is understood as a complex symbiotic network with bidirectional communication, the gut-brain axis. The implication of this communication involves an intense focus of research on a variety of chronic psychiatric, neurological, neurodegenerative, and neuro-oncological diseases. Recently, the gut-brain axis has been studied in neurologically ill patients requiring intensive care. Preliminary studies have shown that acute brain injury changes the bacterial phenotype from one that is symbiotic with the host human to one that is pathologic, termed the "pathobiome." This can contribute to nosocomial pneumonia and sepsis. The first studies in neurologically ill patients in the neurointensive care unit (neuroICU) demonstrated changes in the gut microbiome between neuroICU patients and healthy matched subjects. Specifically, a decrease in short-chain fatty acid-producing bacteria and increase in harmful gut microbes have been associated with mortality and decreased function at discharge. Although these preliminary findings are exciting and have opened a new field of research in the complex neuroICU population, there are several limitations and challenges. Further investigation is needed to confirm these correlations and understand their implications on patients in a complex intensive care environment.

**Keywords:** Neurocritical care; Microbiome; Brain-gut axis; Nosocomial infection

## INTRODUCTION

The development of next-generation sequencing technologies has enabled the study of the gut microbiome. The gut microbiome comprises all living organisms that inhabit the human gut. When a human being is healthy, the host and microbiome live symbiotically. In this scenario, the host provides nutrients and an environment for the bacteria to thrive, and the bacteria supply necessary nutrients back to the host [1-3]. This relationship is forged between the brain via the gut-brain axis: a bidirectional communication through fecal metabolites such as neurotransmitters and short-chain fatty acids (SCFAs), the autonomic nervous system

(ANS; vagus nerve), and neuroendocrine pathways [4].

Although studies have examined the role of microbiota in a variety of chronic neurological diseases [1-3,5-11], studies on the role of the microbiome in patients with acute brain injury are in their infancy. Recent studies on the gut microbiome in neurocritically ill patients needing care in the neurointensive care unit (neuroICU) have revealed that the gut microbiome is an important factor in disease processes and prognosis of these patients [12-14]. In this review article, we summarize and introduce the concept of the gut microbiome and disease, the gut-brain axis, and its relationship with neurologic diseases in critically ill patients. We highlight the possible implications of the gut-brain axis on patients in the intensive care unit (ICU) and neuroICU and comment on future research areas and their challenges.

## GUT MICROBIOME

The gut microbiome, often referred to as the forgotten organ, comprises the microbes that inhabit the gastrointestinal tract. These microbes are more than 10 times as common as the human cells in our bodies and constitute over 150 of the genes of our human genome [4,15]. It is estimated that the adult gut microbiome comprises up to 1,000 species, of which *Bacteroidetes* and *Firmicutes* are the two predominant phylotypes [16,17]. The gut microbiome is established early in life and is susceptible to multiple factors, including diet, ethnicity, and age [18-20]. The gut microbiome and its associated genes and products coexist in a homeostatic ecosystem within their host [20].

The functions of the gut microbiome include immune activation and response modulation, epithelial barrier integrity, nutrient absorption and storage, conversion of luminal compounds to metabolites, host-bacterial interactions on the mucosal surface, and long-term behaviors and brain process modulation [5,20-24]. Since the microbiome plays a critical role in the normal physiological function of the gut, multiple studies have pursued the establishment of the taxonomic composition and structure of this microbiome's constituents in healthy individuals. However, the definition of a "normal" gut microbiome remains inconclusive given the high compositional variability of the microbial taxa, even within healthy individuals and their family members [18,25,26]. However, the genes encoding specific metabolic functions and regulatory pathways are largely conserved [18,20,25,27].

The disruption of the composition and, therefore, the normal function of the microbiome is called dysbiosis. This dysbiosis can be the product of many pathological states, but is usually the product of antibiotics, dietary changes, or a lack of bacterial diversity [20,28]. Dysbiosis is a crucial aspect of the gut microbiome, given that this state increases the host's susceptibility to the disease owing to its inability to effectively respond to environmental changes [29]. However, whether dysbiosis is a response to or the cause of a particular disease state remains uncertain [20,29].

### Microbiome sequencing

The development of two specific techniques, 16S ribosomal RNA (16S rRNA or 16S rRNA) and whole-genome shotgun sequencing (WGS) have enabled us to study the microbiome in greater detail. Both the techniques are similar and provide complementary information. The 16S gene sequencing is mostly used in identifying the microbiome's bacterial composition. The 16S rRNA has nine variable regions (V1-V9), which distinguish individual bacterial taxa from extracted bacterial DNA. When processed, the DNA sample is amplified by polymerase chain reaction and compared to a known bacterial library to identify the lowest taxonomic levels [30]. While WGS is more expensive and demanding, it provides data on strain-level resolution and functional capacity, characteristics that cannot be obtained with 16S sequencing. In WGS, all DNA in a sample are sequenced using next-generation sequencing. WGS has some advantages over 16S, including the lack of polymerase chain reaction amplification, entire genome sequencing, and strain resolution, which allows greater inference of the gut microbiome [31]. Conversely, the advantages of 16S include a lower cost, the avoidance of host DNA contamination, and the capability to sequence with lower quantities of genetic material [30,31]. After taxonomic assignment, the bacterial composition is frequently evaluated in terms of alpha diversity (within-sample) and beta diversity (between-sample). Alpha diversity is a measure of the species diversity within a sample. This summarizes its richness and uniformity [32]. Beta diversity describes the species diversity between two or more microbial communities in different samples. Bioinformatic tools for visualizing and comparing the diversity and abundance of the microbiome are being developed. Some methodologies can also predict the biological functions of specific microbiome taxa [33].

### Metabolomic analysis

Metabolomic analysis, also known as metabolite or metabolomic analysis, refers to the evaluation of metabolites (vitamins, fatty acids, amino acids, and bile acids) produced or regulated by the gut microbiome. In contrast to classic biochemical approaches that evaluate single compounds, metabolomic analysis evaluates a broader series of metabolites to obtain a holistic understanding of the interactions between the microbiome and the condition studied [34]. Different instruments and software exist for metabolom-


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ic analysis, depending on the goal of the study, including liquid chromatography with colorimetric array detection, gas chromatography with mass spectrometry, and liquid chromatography-mass spectrometry. The latter is commonly used because of its large biochemical profile in biological samples, especially in gut microbiome studies [34,35]. In gut microbiome metabolomic analysis, the samples are collected, and small molecules are isolated from the sample and analyzed using one of the previously mentioned techniques. After the collection of data, they have to be curated and analyzed using the appropriate software to discover relevant biochemical pathways involved in the gut microbiome brain axis [10].

## GUT MICROBIOME BRAIN AXIS

Bidirectional communication between the enteric nervous system and the central nervous system (CNS) forms a network called the gut-brain axis, which is a relatively new but increasingly accepted concept [4]. Gut microbiome dysbiosis was initially studied in diseases related to the gastrointestinal tract, such as irritable bowel syndrome [24]. However, a growing body of evidence reveals that gut microbiome dysbiosis has pathophysiological effects on the CNS [4,24,36]. Preclinical studies have shown that by using gut microbiome manipulation with germ-free, antibiotic-induced depleted, prebiotic/probiotic supplementation, and fecal microbiota transplant animal models, changes in the gut microbiome can alter brain signaling and function including neurotransmitter receptor expression, memory dysfunction, alterations in neuron excitability, and others [36-39]. The translation of these preclinical studies to human populations has been challenging, given the complexity of changes in the human gut microbiome and inter-individual gut microbiome differences. One approach to studying the effects of the gut microbiome on the brain has been to utilize brain imaging to correlate microbial ecology with various neural networks [5,24]. Manipulation of the gut microbiome using antibiotics has shown increased subcortical and frontoparietal brain connectivity, as well as improved cognitive function in a small cohort of minimal hepatic encephalopathic patients [40]. Although preliminary, this suggests that changes in the gut microbiome affect networks in the diseased brain.

The gut microbiome affects neurological function via multiple pathways, including neuroendocrine and immunological pathways, whereas the brain affects the composition of the gut microbiome via the ANS [24]. The ANS has both central and peripheral neurons, which create a brain-gut loop with constant feedback from afferent and efferent fibers. In association with the enteric nervous system, the ANS can induce changes in the gut that affect the gut microbiome, such as gut motility and mucus secretion [5,24]. Most communication depends on the vagus nerve. The vagus nerve afferent neurons provide signals from several gut layers to the nucleus tractus solitaries of the brain, which then act as an emissary of these gut-derived signals to the brain. On the other end, the integrated parasympathetic response is then conducted back through the vagus nerve, producing physical and behavioral changes [5,41]. Sympathetic innervation through less direct pathways primarily serves as the intestinal mucus layer integrity maintenance [42]. The sympathetic ANS is affected by bacterial metabolites in germ-free and antibiotic-treated mice. In this scenario, the SCFA-producing bacteria have a suppressive effect on sympathetic ascending signaling [43].

Another important route through which the gut-brain axis communicates is through gut bacteria-derived metabolites. The gut microbiome regulates metabolite levels by modulating metabolites reactions [23]. SCFA levels have been identified in the cerebrospinal fluid and brain tissue, and these have been associated with numerous CNS diseases [5,10]. SCFAs broadly impact the immune response through the regulation of antigen-presenting cells and production of interleukin-10, TH-1, and TH-17 production [44]. The microbiome also produces and reacts with several neurotransmitters including serotonin, norepinephrine, and other catecholamines. CNS diseases significantly distort fecal neurotransmitter levels outside the physiological range, creating systemic neurotransmitter change [10].

## GUT MICROBIOME AND BLOOD–BRAIN BARRIER

The blood-brain barrier (BBB) comprises an endothelial cell tight junction network that contributes to maintaining CNS homeostasis [45]. The BBB prevents the diffusion of pathogens and hydrophilic molecules from the systemic circulation while permitting the passage of critical gases ($O_2$ and $CO_2$) and lipid-soluble substances (glucose) [45]. BBB disruption is a key mechanism of worsening neurological disease in acute neurological diseases, including traumatic brain injury (TBI) and stroke [46,47]. After the initial brain injury, subsequent breakdown of the BBB leads to the propagation of injury, secondary brain injury, and worsening of clinical outcomes. In both preclinical and clinical settings, increased BBB permeability is a marker of disease progression and a therapeutic target [48].

Studies have shown that the gut microbiome influences the development and maintenance of the BBB tight junctions. Germ-free mice (mice without normal gut microbiome flora) have reduced occludin and claudin-5 expression, key BBB tight junction

regulators, resulting in increased BBB permeability [49]. These changes started intrauterine and were maintained after birth, demonstrating the importance of the gut microbiome in BBB formation and maintenance. Furthermore, gut colonization of germ-free mice with microbiomes reverses the effects seen in the BBB due to the lack of gut microbiome [49]. Recent studies have further confirmed the relationship between the BBB and the gut microbiome, Wen et al. [50] showed that postoperative cognitive deficits in mice can be aggravated by the administration of antibiotics. Mice that were administered antibiotics showed decreased expression of tight junctions, consequently increasing the BBB permeability. The BBB alterations could be overturned by the administration of *Lactobacillus* and sodium butyrate [50]. The effects of gut microbiome composition and the function and permeability of the BBB were further tested in adult mammals by Wu et al. [51]. Rhesus monkeys treated with oral amoxycillin-clavulanic acid had increased permeability of the BBB, as measured by the albumin ratio in the cerebrospinal fluid/serum. This was attributed to the detrimental effect of oral antibiotics on acetic acid-and propionic acid-producing microbiome [51]. Although these preclinical findings are exciting given the possibility of BBB modulation in several CNS diseases, their translation remains untested. Fig. 1 shows the gut microbiome and BBB modulation according to the studies presented.

## GUT-BRAIN MICROBIOME AND CNS DISEASES

Accumulating evidence implicates the gut microbiome in various psychiatric, neurological, neurodegenerative, and neuro-oncological diseases [1-3,5-11]. However, the level of evidence varies depending on the disease. Some are still in the preliminary stage, with limited correlational observations, while others provide stronger evidence for a causal role in the disease [5]. The relationship between multiple sclerosis and autism spectrum disorder (ASD) and the gut microbiome has been thoroughly investigated

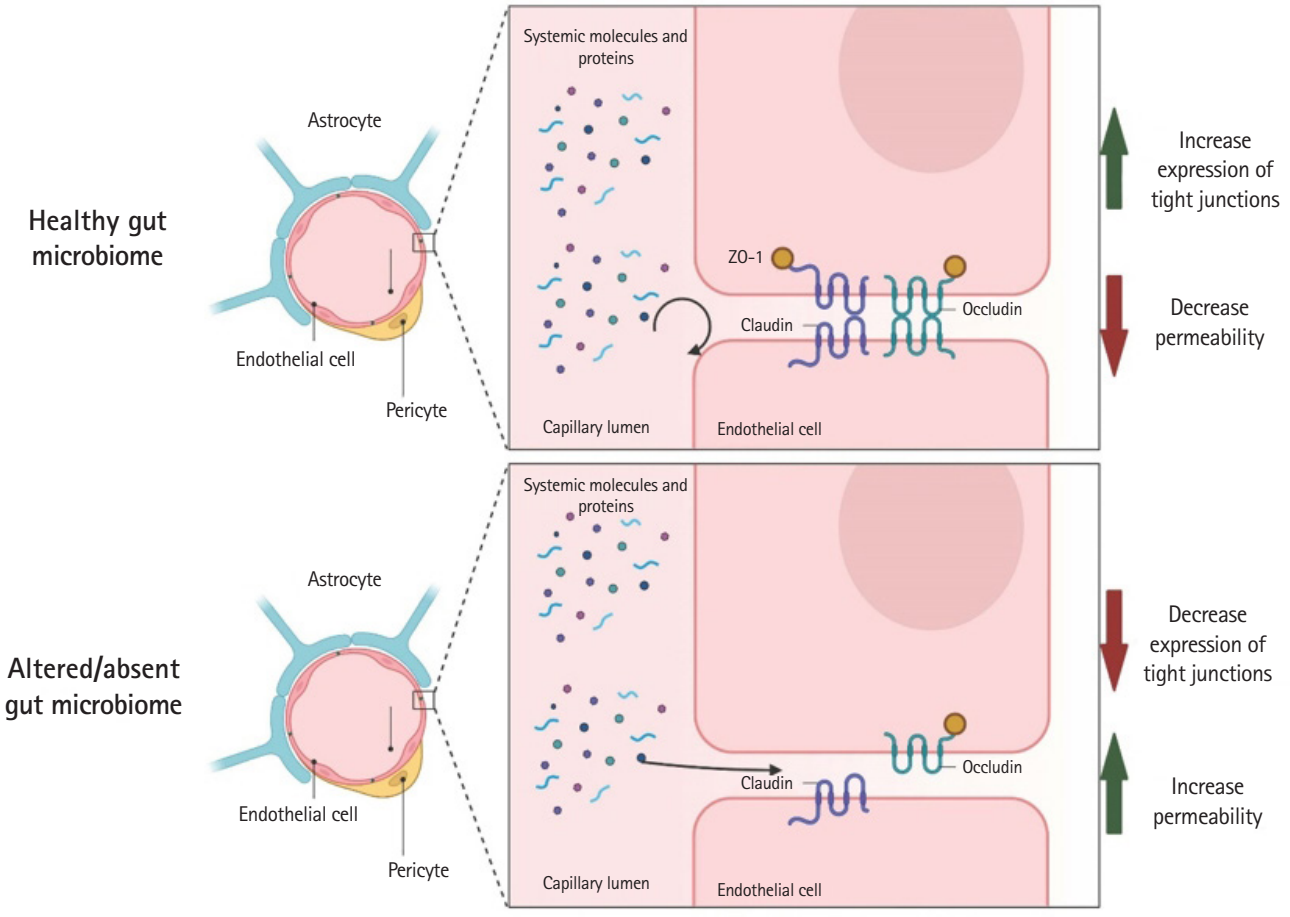


**Fig. 1.** Gut microbiome affects the blood-brain barrier. Animal (mice and monkey) studies have shown that the alteration or absence of the gut microbiome (germ-free or antibiotic-induced) decreased tight junction (occludin and claudin) expression in the blood-brain barrier by an unknown mechanism. This figure was created by authors using BioRender (https://www.BioRender.com).


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in both animals and humans [3,8,52,53]. In ASD, recent studies have demonstrated that fecal microbiome transplantation is effective in improving gastrointestinal and behavioral symptoms [54]. Moreover, a placebo-controlled study showed that a casein/gluten-free diet combination, along with prebiotic B-GOS, led to behavioral improvement in children with ASD. This was accompanied by a relative increase in the abundance of *Bifidobacterium longum* [55]. A recent study showed a higher abundance of *Akkermansia muciniphila* and *Acinetobacter calcoaceticus* in fecal samples of multiple sclerosis patients [56]. Another recent study showed that *A. muciniphila* and its associated nicotinamide improved amyotrophic lateral sclerosis symptoms and gene expression patterns, while *Ruminococcus torques* and *Parabacteroides distasonis* worsened the amyotrophic lateral sclerosis symptoms [2]. In Alzheimer disease, the gut microbiome is related to β-amyloid plaques and the pathophysiology of the disease [57]. Other interesting findings have correlated epilepsy and Parkinson disease outcomes due to specific microbial-derived metabolites or drug metabolism from bacteria [58,59]. Moreover, psychiatric diseases as well as neuro-oncological entities have been associated with the gut microbiome [5,10,11,60]. In animal models of stroke, several studies have shown the role of the gut microbiome through the modulation of SCFAs [1,61]. Recent studies have shown that the gut microbiome directly impacts the risk of thrombotic events, including strokes, through the production of trimethylamine N-oxide (TMAO), a gut microbe-dependent metabolite produced from precursors known in Western diets (e.g., choline, phosphatidylcholine, carnitine) [62]. TMAO exposure augments intracellular calcium in platelets, with a subsequent increase in thrombosis. This process is dependent on the metabolism of dietary choline and other precursors [62]. Although these studies have shown a strong correlation between multiple CNS diseases and the gut microbiome, much remains to be discovered, especially the causality of the observed changes.

## GUT MICROBIOME IN NEUROCRITICAL CARE

The gut microbiome profile of severely ill patients requiring ICU care has only been studied in the last decade. Patients with systemic inflammatory response syndrome with decreased obligate anaerobes and increased pathogenic bacteria showed correlation with septic complications and mortality [63]. Further research has demonstrated that even though the gut microbiome of septic and non-septic critically ill patients is highly heterogeneous, it suffers from low diversity, and is typically colonized by pathogenic microbes (e.g., *Enterobacterales*, *Staphylococcus*, *Enterococcus*, or yeasts) in contrast to a more physiologic gut microbiome [64-66]. This loss of the "normal" gut microbiome generates the absence of important host metabolism functions [65]. Moreover, an increased dysbiosis, measured by the relationship between the two more abundant gut microbiome phyla, *Firmicutes* and *Bacteroides*, and the *Firmicutes*: *Bacteroides* ratio has been observed in a small prospective cohort of ICU patients [67]. Another potential biomarker of dysbiosis, the gut colonization with *Enterococcus* [68], has been shown to be closely associated with survival when this bacterium is identified upon admission to the ICU [68,69].

Healthcare-associated infections are one of the many prognostic factors in critically ill patients, including neuroICU patients. This can occur in up to 25% of ICU patients and have significant effects on morbidity and mortality [70]. Rectal or throat colonization by pathogenic bacteria increases the risk of further infection (e.g., pneumonia) with the same pathogen [69,71,72]. In this context, the role of the gut microbiome in the development of pneumonia has been investigated in animal models [73] as well as in the pathogenesis of ICU patients with ventilator-associated pneumonia [74]. Dickson et al. [12] showed that the lung microbiome is enriched with gut microbes in both mouse models and patients with established acute respiratory distress syndrome (ARDS). Additionally, their experiments established that lower gastrointestinal tract bacteria, rather than the upper respiratory tract bacteria, were the culprit of post-sepsis lung infection. Furthermore, *Bacteroides* were frequently detected in ARDS patients and are associated with the intensity of systemic inflammation [12].

Sepsis, a term used since the time of Hippocrates, has been defined as an infection that provokes life-threatening organ dysfunction [75] and is a common disease worldwide with major repercussions in morbidity, mortality, quality of life, and medical costs for both inpatients and outpatients [76]. The incidence of sepsis is estimated to be 288 per 100,000 person-years in hospital-treated sepsis, whereas hospital mortality is estimated to be 17% for sepsis and 26% for severe sepsis [77]. In the neuroICU, sepsis is a leading cause of morbidity and mortality [78,79]. Although population studies are scarce, some studies estimate it as 1.4%–12.6% of patients admitted to the neuroICU, and it is invariably associated with worsening prognosis [78,79]. A provocative recent study showed that increased bacterial DNA can be identified in the brain after sepsis in both murine models and human patients. These brain-associated bacteria correlate with neuroinflammation and are likely associated with acute brain dysfunction in sepsis [13].

The importance of the gastrointestinal tract in neurological intensive care has been known since the observation of Carl Roki-

tansky in 1841 and the later classic work of Harvey Cushing regarding the relationship between intracranial pressure and gastric and proximal duodenal ulcers [80,81]. Other known gastrointestinal syndromes that commonly affect neuroICU patients include acute colonic pseudo-obstruction and other motility problems, given the severity of neurological illnesses and the use of medications with gastrointestinal side effects such as opioids and other anticholinergic drugs [82]. Despite the known relationship between neurocritically ill patients and gastrointestinal diseases and the well-known gut microbiome brain axis studies in multiple neurological diseases, little is known about the gut microbiome in the neuroICU population. The first dedicated studies evaluating the microbiome of neurocritically ill patients are the initial steps toward understanding the role of the gut microbiome in the disease process and the mechanisms of neurological patients requiring ICU treatment. This understanding is the first step toward the identification of possible microbiome modulation that affects prognosis. Xu et al. [14] observed a distinct gut microbiome between neuroICU patients and healthy controls. Alpha diversity and the abundance of known SCFA producer bacteria like *Ruminococcaceae* and *Lachnospiraceae* were significantly reduced during the hospital stay in neurocritically ill patients. Similar to other studies on critically ill patients [68], Xu et al. [14] showed that neuroICU patients with increased *Enterobacteriaceae* (family *Enterococcus*) during their first week of hospital stay had increased 6-month mortality after adjustment for multiple factors. Moreover, an association between *Enterobacteriaceae* and the modified Rankin scale score at discharge was noted [14]. Although this study represents an important effort to understand the relationship between the gut microbiome and outcomes in neuroICU patients, it has several limitations, including the lack of data regarding antibiotic utilization as well as the heterogeneity of the patient

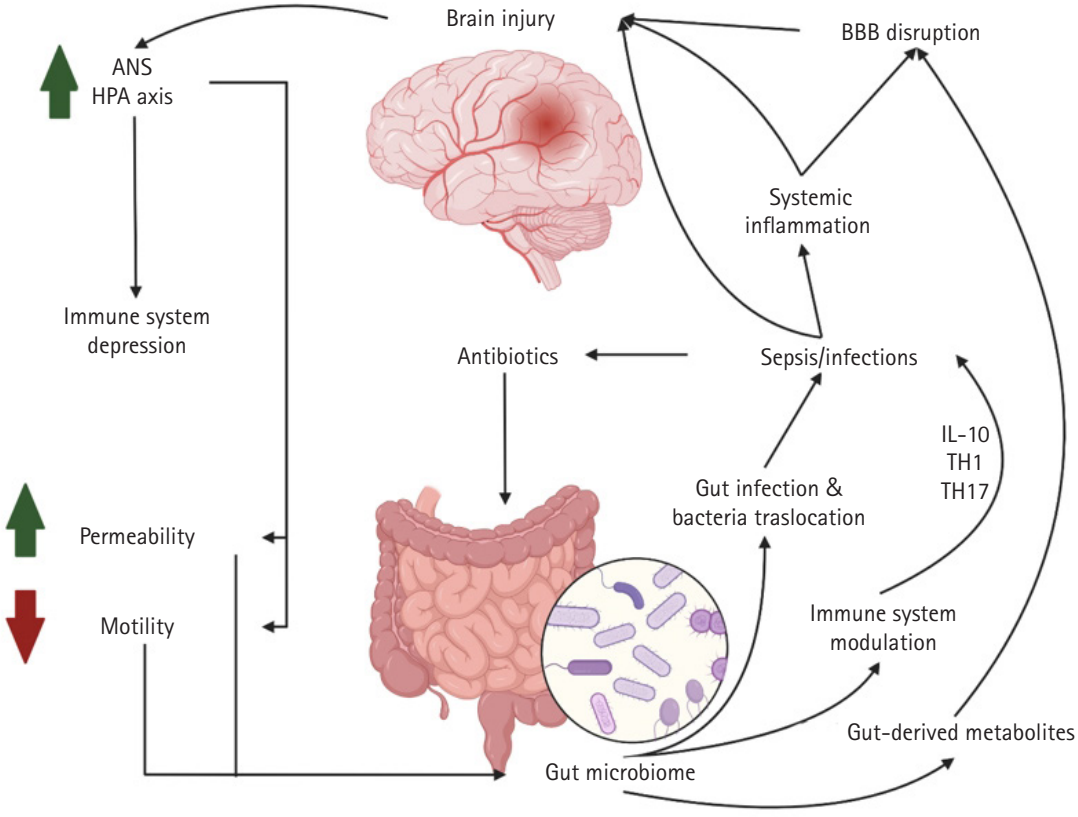


**Fig. 2.** Gut-brain axis in neurocritically ill patients. We hypothesize that patients with severe brain injury (e.g., traumatic brain injury or intraparenchymal hemorrhage), may have dysregulation of the autonomic nervous system (ANS) and hypothalamic-pituitary-adrenal (HPA) axis which could lead to immune system depression, increased gut permeability, and decreased motility. These changes result in gut microbiome dysbiosis, which facilitates infection and bacterial gut translocation, as well as immunosuppression, thereby predisposing individuals to infections and sepsis. An infectious state produces systemic inflammation that promotes blood-brain barrier (BBB) disruption and additional brain injury, secondary to inflammation. Additionally, antibiotic treatment against previously mentioned infections promotes gut dysbiosis. Another mechanism of BBB disruption leading to additional brain injury are gut-derived metabolite changes that are secondary to gut microbiome dysbiosis. IL-10, interleukin-10. This figure was created by authors using BioRender (https://www.BioRender.com).


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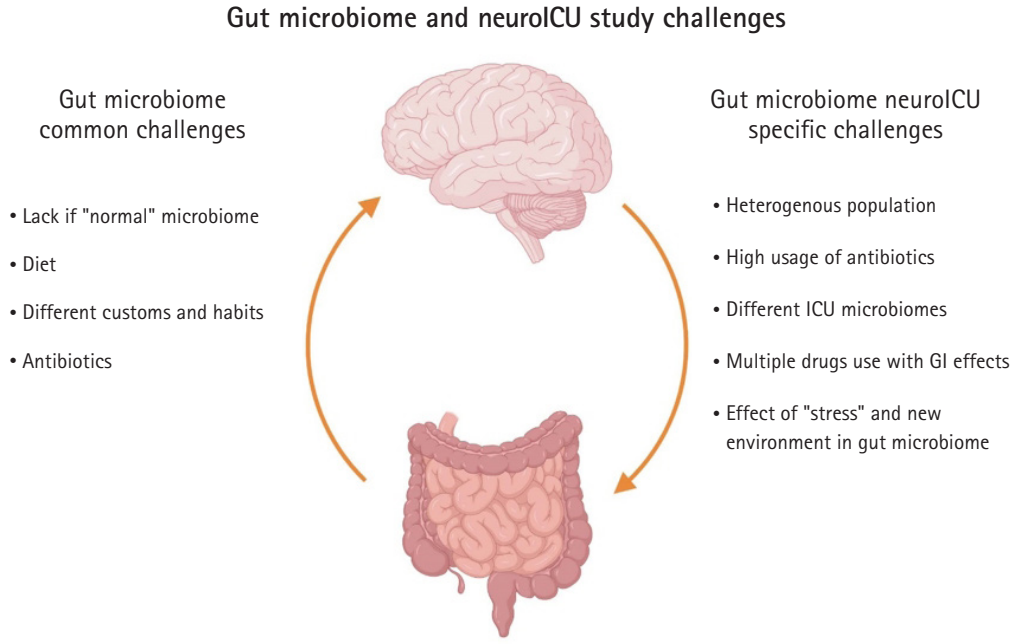


**Fig. 3.** Challenges of gut microbiome studies in the neurointensive care unit (neuroICU). ICU, intensive care unit; GI, gastrointestinal. This figure was created by authors using BioRender (https://www.BioRender.com).

population. A summary of the gut-brain axis relationship in brain injury is shown in Fig. 2.

## FUTURE DIRECTION AND CHALLENGES

The gut microbiome in neuroICU patients is an emerging topic of research that requires further investigation. Since research efforts have been performed to elucidate the gut microbiome relationship in multiple CNS diseases (e.g., stroke, brain tumors, epilepsy, or TBI) and a growing body of evidence has shown that the gut microbiome influences common neuroICU comorbidities such as ventilator associated pneumonia and sepsis, we foresee that this topic will become more relevant with the continuity of research efforts. To date, the few published studies have been limited to assessing correlations, for example, Enterobacteria and pneumonia/sepsis; however, future studies should seek to answer more questions pertaining to causality, such as whether the eradication of the pathobiome or restoration of a healthy microbiome through gut manipulation (probiotics, prebiotics, fecal transplants) improves morbidity or mortality.

Addressing these questions can open innovative therapeutic avenues for neurocritically ill patients, as established in other diseases such as *Clostridium difficile* infections [83], or enhance known therapies, as shown in the first human clinical trials of fecal transplant to overcome anti-PD-1 (programmed death-ligand 1) resistance in melanoma [84,85]. These and other gut microbiome therapeutic strategies have revolutionized our understanding of our interactions with the microbiome that inhabits us.

Some challenges of studying the gut microbiome in neuroICU patients are common to gut microbiome studies, such as the lack of a "normal" gut microbiome and differences in the gut microbiome associated with diet and customs. However, other challenges are specific to the neuroICU population, which include a heterogeneous population (TBI, stroke, brain tumors, subarachnoid hemorrhages), high usage of antibiotics, different ICU biomes, and the difficulty of assessing whether the microbiome changes are due to the disease itself, the ICU environment, or medications (Fig. 3).

## CONCLUSIONS

The gut-brain axis is a bidirectional communication through several pathways, a symbiotic relationship that can be affected by both microbiome changes to pathogens and CNS diseases. The role of the gut microbiome in CNS diseases has been actively studied, but remains an area of limited knowledge.

## ARTICLE INFORMATION

**Ethics statement**

Not applicable.

**Conflict of interest**
Huimahn A. Choi is an editorial board member of the journal but he was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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**Author contributions**
Conceptualization: HAC. Methodology: all authors. Project administration: HAC. Visualization: AD. Writing–original draft: AD, HAC. Writing–review & editing: all authors.

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ORIGINAL ARTICLE

# Prevalence and outcomes of acute respiratory distress syndrome in patients with aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis

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**Background:** In this study, we aimed to investigate the prevalence, timing, risk factors, and outcomes of acute respiratory distress syndrome (ARDS) in patients with aneurysmal subarachnoid hemorrhage (aSAH).

**Methods:** PubMed and four other databases were searched for randomized controlled trials (RCTs) and observational studies of patients 18 years or older through October 20, 2021. Study quality was assessed, using the Cochrane Risk of Bias tool for RCTs and the Newcastle-Ottawa scale for cohort and case-control studies. High-grade aSAH was defined as a Hunt-Hess grade ≥3 and/or a modified Fisher score ≥3. A good neurological outcome was defined as a Glasgow outcome scale score ≥4. Random-effects meta-analyses were conducted to estimate the pooled outcome prevalence and 95% confidence interval (CI).

**Results:** Eleven observational studies (n=6,107) met the inclusion criteria. Overall, 15% of the patients (95% CI, 10.5–20.0; $I^2$=97.8%) developed ARDS after aSAH, with a mean time of 3 days (95% CI, 1.9–3.7; $I^2$=54%). Overall survival at discharge was 80% (95% CI, 75–86; $I^2$=96%), and 67% of aSAH patients (95% CI, 54.9–78.9; $I^2$=94%) had a good neurological outcome at any time. The aSAH cohort without ARDS had a higher rate of survival than those with ARDS (79% vs. 49%, $P$=0.028). Male sex, patients with a high-grade aSAH, patients who developed pneumonia, and systemic inflammatory response syndrome during hospital admission were at a higher risk of developing ARDS.

**Conclusion:** In this meta-analysis, approximately one in six patients developed ARDS after aSAH, with a mean time of 3 days from the initial presentation, and ARDS was associated with increased mortality.

**Keywords:** Acute respiratory distress syndrome; Subarachnoid hemorrhage; Intracranial hemorrhage; Acute brain injury; Neurogenic pulmonary edema; Acute lung injury

## INTRODUCTION

Aneurysmal subarachnoid hemorrhage (aSAH) accounts for 3% of all stroke, affecting approximately 30,000–40,000 patients annually in the United States and 600,000 worldwide [1]. Although mortality due to aSAH has decreased in the past two to three decades, the 30-day mortality remains high, at approximately 25%–35% [2]. Non-neurological complications, such as cardiopulmonary injuries and systemic inflammation, are frequently seen in patients with aSAH, and may be responsible for > 10% of the deaths in these patients. Other neurological risk factors include the severity of the initial hemorrhage, the timing of surgical or endovascular intervention, and the presence of delayed cerebral ischemia (DCI) [3].

Acute respiratory distress syndrome (ARDS) is a heterogeneous syndrome that is characterized by diffuse damage in the parenchyma of the lung, which is the result of the lung's innate inflammatory response to an injury, along with non-cardiogenic pulmonary edema due to increased alveolar-capillary vascular permeability and the accumulation of protein-rich edematous fluid, resulting in impaired gas exchange and refractory hypoxemia [4]. At present, the mechanism of ARDS, particularly when it occurs after aSAH, is poorly understood. It is thought, however, to be similar to what occurs in patients with traumatic brain injury, which involves a massive sympathetic storm and systemic inflammation in response to the initial brain injury and intracranial pressure (ICP) crisis, subsequently leading to systemic arterial and pulmonary hypertension, as well as increased vascular permeability and pulmonary edema [5,6].

Increasing evidence shows that pulmonary edema and arterial hypoxemia due to ARDS are significantly associated with poor neurological outcomes, increased mortality, and prolonged hospital stays in patients with aSAH [7,8]. Despite its impact on outcomes and mortality in patients with aSAH, information on the prevalence, timing, and risk factors of ARDS is sparse, and prior studies have reported a wide range of ARDS prevalence, ranging from 11% to 60% of patients with acute aSAH [9,10]. The primary aim of the present study was to investigate the prevalence, timing, risk factors, and outcomes of ARDS in patients with aSAH.

## METHODS

### Search strategy

The present systematic review/meta-analysis was reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11]. We searched five databases for subject headings and controlled vocabulary, as well as keywords and language relevant to acute lung injury (ALI), ARDS, and brain injury, as follows: PubMed, both the legacy (results = 4,991) and new (results = 5,804) databases via The National Center for Biotechnology Information (NCBI); Embase via Elsevier (results = 10,216); the Cochrane Library via Wiley (results = 791); the Web of Science Core Collection via Clarivate (results = 5,249); and Scopus via Elsevier (results = 11,193). The initial search was conducted from the inception of the databases through July 6, 2020. An updated search was performed on October 20, 2021. There were no language limitations to this study, and all efforts were made to account for plural words, acronyms, and synonyms. In total, 38,194 results were obtained, from which 20,151 duplicates were removed, leaving 18,043 results. Data deduplication was performed using EndNote X9 (Endnote, Clarivate; available at https://www.endnote.com), after which the results were uploaded to Covidence (Veritas Health Innovation, Melbourne, Australia; available at https://www.covidence.org) for title and abstract screening, and were further reviewed for eligibility. All articles that met the inclusion criteria were retrieved, and the full texts were reviewed. References from the included studies were also manually reviewed to search for additional relevant studies. Supplementary Material 1 presents the details of the search strategy used in our review.

### Study eligibility: inclusion and exclusion criteria

The inclusion criteria were as follows: (1) all randomized controlled trials (RCTs) and observational studies with adult patients (> 18 years old); and (2) studies involving ALI or ARDS, as defined by either the American-European Consensus Conference (AECC) or the Berlin criteria, which occurred after aSAH [12,13]. Studies that reported patients with ALI based on the AECC criteria, defined as a $PaO_2/FiO_2$ (P/F) ratio between 201 and 300, were classified as having mild ARDS for the present study, while patients with a P/F ratio ≤ 200 were classified as having moderate/severe ARDS [12,13]. The exclusion criteria were as follows: (1) editorials, commentaries, research protocols, reviews (including systematic reviews and meta-analyses), case series/reports, abstracts, and articles only available in foreign languages; (2) articles with pediatric populations (< 18 years old); (3) studies without a description or definition of ALI or ARDS; (4) animal and *in vitro* studies; and (5) ARDS that occurred prior to aSAH. Additionally, case-control studies were excluded from the analysis of the prevalence of ARDS after aSAH.

### Study selection and data extraction

The literature results were independently assessed by two reviewers (THF and MH) for eligibility, and any disagreements

on the inclusion or exclusion were resolved by a third reviewer (SMC). Data were extracted from eligible studies and recorded in an Excel spreadsheet (Microsoft, Redmond, WA, USA). Full texts and charts were reviewed in detail for data regarding study design, study population, number of patients with high-grade aSAH (defined based on clinical severity as a Hunt Hess grade ≥3, and radiographic severity as a modified Fisher score ≥3), patient characteristics (age, sex, ethnicity, and baseline comorbidities), complications during the hospital stay, including pneumonia, sepsis, systemic inflammatory response syndrome (SIRS; defined as having ≥2 of the following conditions: temperature <36°C or >38°C heart rate >90 beats/min, respiratory rate >20 breaths/min, and/or white blood cell count >12,000 or <4,000 cells/mm$^3$), ARDS variables (etiology, severity, and P/F ratio), Acute Physiology and Chronic Health Evaluation II (APACHE II) score, neurological outcomes, and survival. The Hunt and Hess grade for SAH severity was used instead of the World Federation of Neurosurgical Societies grading system because it was more commonly reported among the included studies.

### Definition of outcomes

The primary outcome evaluated was the prevalence of ARDS which occurred after aSAH. Secondary outcomes included the timing of ARDS development, survival at hospital discharge, and prevalence of good neurological outcomes of discharged patients at any time after a diagnosis of aSAH (defined as a Glasgow Outcome Scale score ≥4) [14].

### Quality assessment/risk of bias

The Newcastle-Ottawa Scale (NOS) was used to assess the quality of nonrandomized studies and to evaluate the risk of bias in case-control and cohort studies. The NOS scores were based on three indices: patient selection, comparability, and assessment of outcome or exposure [15]. Studies scoring ≥6 points were considered to have a low risk for bias. Publication quality was assessed independently by two investigators (THF and MH), and any discrepancies were resolved by consensus with a third investigator (SMC).

### Statistical analysis

We performed the present systematic review according to the PRISMA guidelines (Supplementary Material 2) [10]. The prevalence of each outcome was calculated for each study based on the number of patients with a specific outcome divided by the total number of patients with SAH. This was then pooled for the meta-analysis including all studies. For all meta-analyses of prevalence, we used random effects models with the inverse variance method, while the restricted maximum likelihood model was used to produce unbiased estimates of variance and covariance parameters. The Sidik-Jonkman estimator was used to calculate tau [16], and the Hartung-Knapp adjustment was used to calculate confidence intervals (CI) [17]. The Freeman-Tukey double arcsine transformation was used to calculate the prevalence for all outcomes.

Heterogeneity was assessed using the Cochrane Q statistic (chi-square test), and the magnitude of the heterogeneity was evaluated using the $I^2$ statistic [18]. $I^2$ quantified the degree of heterogeneity in a range of 0%–100% where 0%–40% indicates insignificant heterogeneity, 30%–60% indicates moderate heterogeneity, and 75%–100% indicates considerable heterogeneity. The following patient variables were evaluated for their association with the outcomes of ARDS, using the Mann-Whitney *U*-test for continuous variables and Fisher's exact test for categorical variables: age, sex, presence of high-grade aSAH on initial presentation, presence of pneumonia, sepsis, SIRS, and DCI during hospital admission. A *P*-value <0.05 was considered to be statistically significant. For the present study, a meta-regression analysis was not performed, due to insufficient data. The analysis was performed using STATA 17 (StataCorp., College Station, TX, USA).

## RESULTS

As indicated above, our search yielded 18,043 results after data deduplication. After title and abstract screening, 284 articles were found to be eligible for a full-text review, of which 273 were excluded based on the aforementioned exclusion criteria, leaving a total of 11 studies (n=6,107) to be included in the present study. Fig. 1 shows a flowchart of the selection process. The studies included five prospective (n=4,219) and six retrospective cohort studies (n=1,888). Details of the included studies can be found in Supplementary Table 1. The references for the included studies have been provided in Supplementary Material 3.

### Risk of bias assessment

No RCTs were included in the present systematic review and meta-analysis. The NOS was used to evaluate the included observational studies, which did not indicate a high risk of bias for any of the studies, which had a median NOS score of 7 (Supplementary Table 2).

### Prevalence and timing of ARDS after aSAH

Of the 6,107 patients with aSAH included in the present systematic review and meta-analysis, the median age was 55 years (inter-


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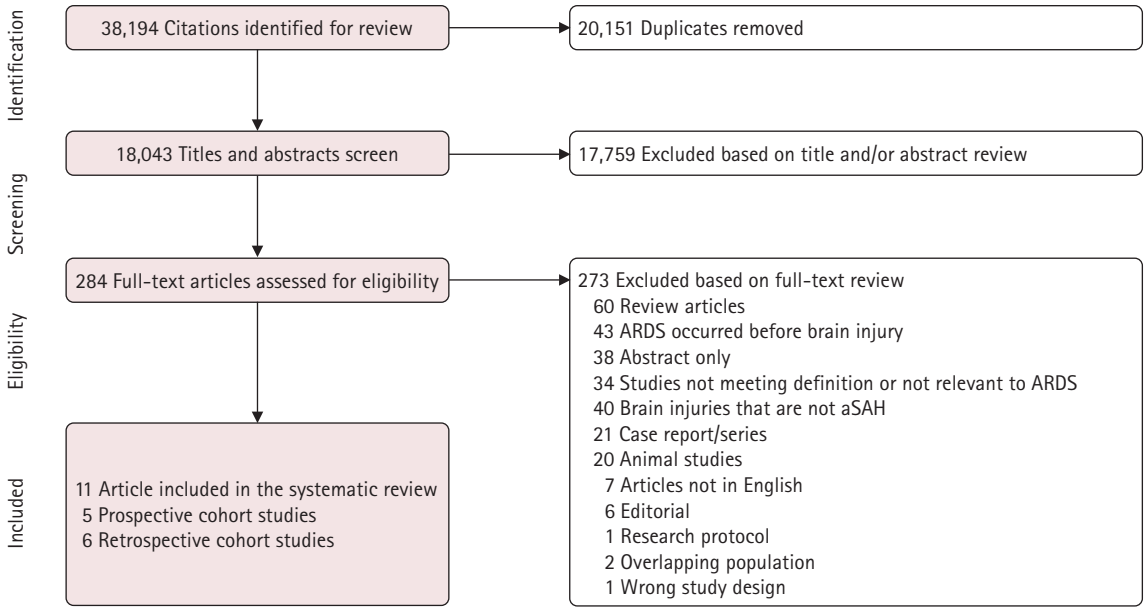


**Fig. 1.** Study flowchart for the literature search and selection of studies. ARDS, acute respiratory distress stress; aSAH, aneurysmal subarachnoid hemorrhage.

quartile range, 52–58 years), and 35% were male (n = 2,107). In this aSAH cohort, 39% of the patients had high-grade aSAH, 19% had sepsis, 11% had pneumonia, and 28% had SIRS. The pooled prevalence of patients who developed ARDS after aSAH was 15% (95% CI, 10.5–20.0; $I^2 = 97.8\%$) (Fig. 2) [8,19-28], and the mean time from the initial aSAH diagnosis to the development of ARDS was 3 days (95% CI, 1.9–3.7; $I^2 = 54\%$) (Fig. 3) [8,20,21,26-28]. An analysis of studies published prior to 2012, which used AECC for ARDS, compared to those published after 2012, which used the Berlin criteria for ARDS, showed no significant difference in the prevalence of ARDS (7% vs. 8%). Of the 11 included studies, 6 (n = 1,567) reported the number of patients with mild ARDS, the pooled prevalence of which was 9.78% (95% CI, 6.3–13.2; $I^2 = 81\%$) (Supplementary Fig. 1), while seven studies (n = 1,923) reported the number of patients with moderate/severe ARDS, the pooled prevalence of which was 13% (95% CI, 7.8–15.3; $I^2 = 93\%$) (Supplementary Fig. 2).

### Risk factors for ARDS in patients with aSAH

Of the 11 included studies, five (n = 2,313) reported the characteristics of patients with and without ARDS. The univariate analysis of the five studies showed that male sex (odd ratio [OR], 2.07; 95% CI, 1.5–2.8; $P = 0.04$), high-grade aSAH (OR, 2.5; 95% CI, 1.8–3.5; $P = 0.02$), the presence of pneumonia (OR, 4.4; 95% CI, 2.6–7.2; $P = 0.01$), and SIRS (OR, 16.3; 95% CI, 5.5–48.7; $P = 0.02$) during hospital admission were associated with a higher risk of developing ARDS in patients with aSAH. Sepsis and DCI were not found to be associated with an increased risk of ARDS (Supplementary Table 3).

### Survival and neurological outcomes

A total of 10 studies (n = 4,922) reported the number of in-hospital survivors of aSAH. The pooled overall survival at discharge after aSAH was 80% (95% CI, 75–86; $I^2 = 96\%$) (Fig. 4) [8,19-26,28], and we found that the survival rate was significantly lower in the aSAH cohort with ARDS than in those without (49% vs. 79%; OR, 0.24; 95% CI, 0.17–0.33; $P = 0.028$).

Of the 11 included studies, six (n = 3,939; 78%) reported the neurological outcomes after aSAH. Good neurological outcomes at any time were achieved in 67% of the patients with aSAH (95% CI, 54.9–78.9; $I^2 = 98\%$) (Fig. 5) [21,23,25-27,29]. Two studies (n = 947) compared the neurological outcomes between patients with and without ARDS, and the ARDS group had significantly fewer patients with good neurological outcomes at any time after aSAH (25% vs. 61%; $P < 0.001$).

## DISCUSSION

To the best of our knowledge, this is the first systematic review and meta-analysis to evaluate the prevalence, timing, risk factors, and outcomes of ARDS after acute aSAH. The results of our study, which included 6,107 adult patients with aSAH, demonstrated a high prevalence of ARDS (15%) in this population. Unsurprisingly, we found that the development of ARDS after aSAH

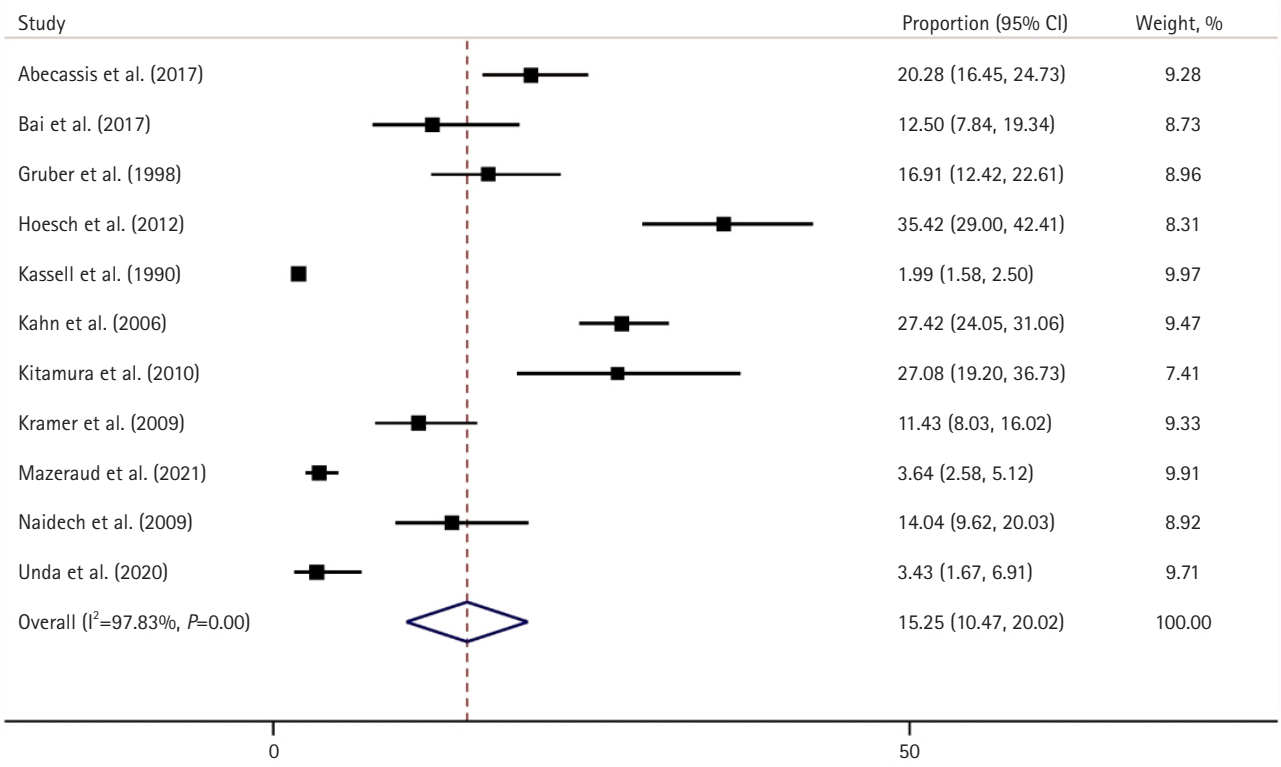


**Fig. 2.** Meta-analysis of the prevalence of acute respiratory distress stress among patients with aneurysmal subarachnoid hemorrhage. $I^2$ quantifies the degree of heterogeneity across the studies, and ranges from 0% to 100%. CI, confidence interval.

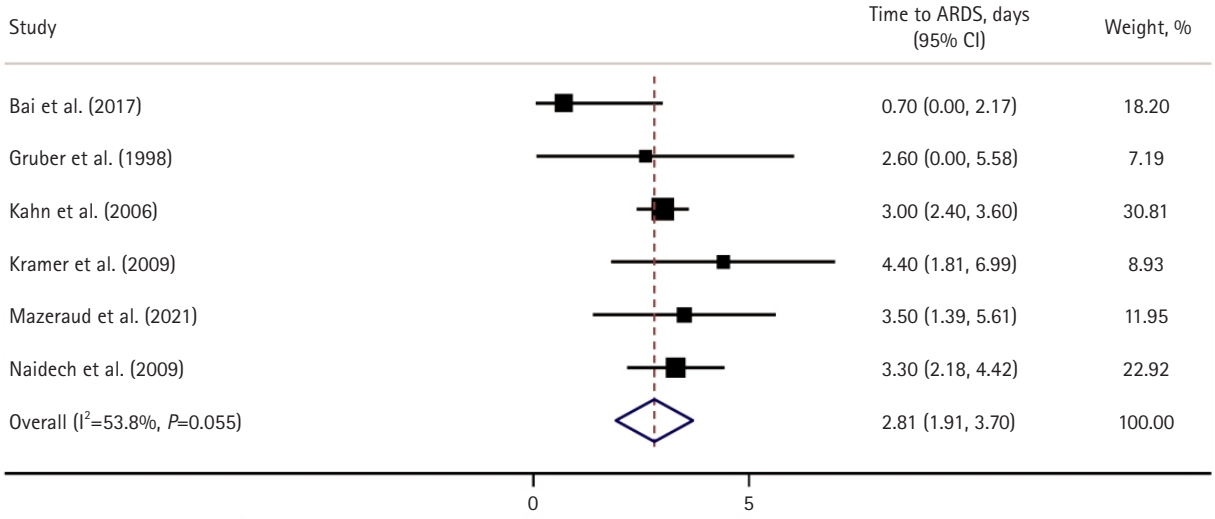


**Fig. 3.** Meta-analysis of the time in days from diagnosis of aneurysmal subarachnoid hemorrhage to the onset of acute respiratory distress stress (ARDS). $I^2$ quantifies the degree of heterogeneity across the studies, and ranges from 0% to 100%. CI, confidence interval.

is associated with a 4-fold increased risk of mortality.

Interestingly, the mean time of development from aSAH to ARDS was 3 days, which highlights the important connection between the brain and the lungs, suggesting that the catecholamine surge and systemic inflammatory response after the onset of aSAH may be responsible for causing ARDS shortly after the initial injury, rather than infectious complications such as pneumonia. Although preclinical studies aiming to understand the mechanisms of aSAH-associated ARDS are sparse, neurogenic edema is a known cause of acute respiratory failure following aSAH [29,


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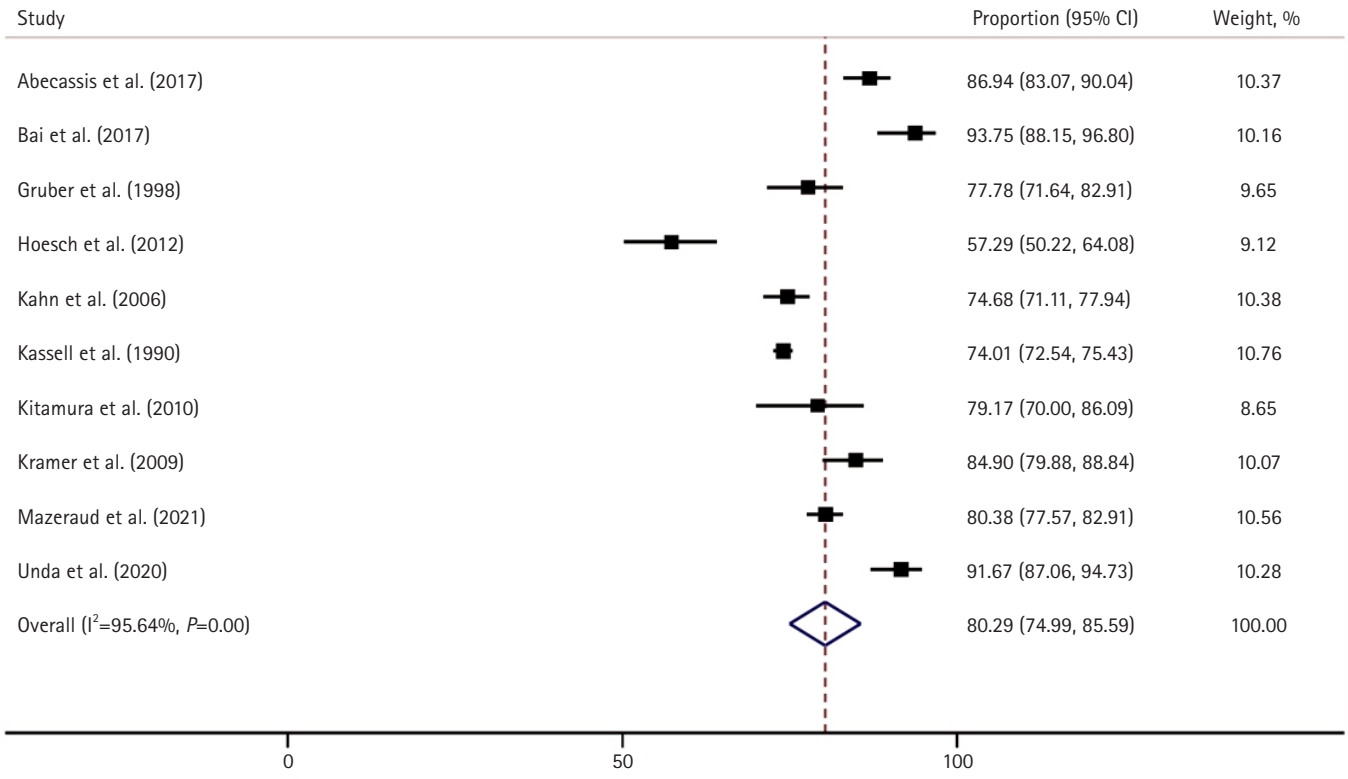


**Fig. 4.** Meta-analysis of overall survival at discharge in patients with aneurysmal subarachnoid hemorrhage. $I^2$ quantifies the degree of heterogeneity across the studies, and ranges from 0% to 100%. CI, confidence interval.

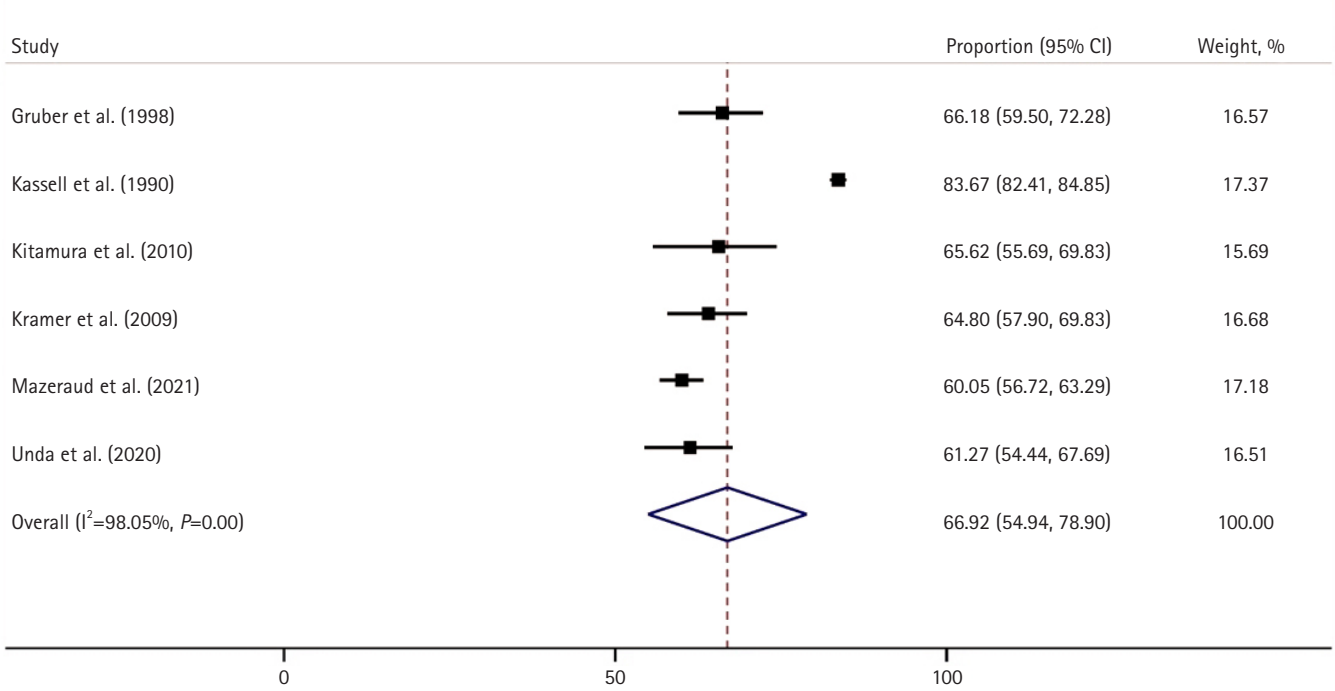


**Fig. 5.** Meta-analysis of overall good neurological outcomes at any time in patients with aneurysmal subarachnoid hemorrhage. $I^2$ quantifies the degree of heterogeneity across the studies, and ranges from 0% to 100%. CI, confidence interval.

30]. aSAH is a significant acute brain injury and insult, which can result in activation of the sympathoadrenal axis with or without elevated ICP, leading to the vasoconstriction of peripheral vessels, elevated systemic arterial pressure, and increased pulmonary hydrostatic pressure, resulting in acute pulmonary edema [31]. Simultaneously, the systemic inflammatory response induced by aSAH can lead to a cytokine storm, causing end-organ damage and increased vascular permeability, which subsequently worsens pulmonary edema and ARDS [6]. Similarly, this massive sympathetic surge can result in stress cardiomyopathy, which can also cause pulmonary edema and imaging findings similar to those of bilateral pulmonary infiltrates, confounding the diagnosis of ARDS. Caution should be taken to rule out cardiogenic pulmonary edema when diagnosing ARDS in conjunction with aSAH [32].

Additionally, the results of the present study indicated that the presence of high-grade aSAH upon initial presentation, as well as the presence of SIRS, were associated with a higher risk of developing ARDS, which further supports the aforementioned hypothesis relating to the interplay between the brain and the lungs. We also found that male sex and the presence of pneumonia were associated with a higher risk of ARDS in patients with aSAH, which highlights that acute brain injury may not be the sole cause for ARDS [8,22,33]. One study found that in addition to developing ARDS within the first 3 days from the onset of aSAH, patient with aSAH can also experience significant deterioration of pulmonary function after day 4 [3,34]. Worsening pulmonary function, along with aspiration due to poor mental status, prolonged intubation, and hospital-acquired pneumonia, may all play a role in the development of aSAH-associated ARDS [34-36]. The early recognition and diagnosis of ARDS in patients with aSAH, as well as the implementation of lung protective ventilation, are important in improving the outcomes of these critically ill patients [37]. The use of lung protective ventilation is often complicated in aSAH patients with elevated ICP, as they may be sensitive to changes in respiratory mechanics and the associated cerebral perfusion pressure [4,5]. Some studies, however, have suggested that positive end-expiratory pressure has no significant effect on cerebral hemodynamics [38,39]. In the present study, we were unable to accurately assess the effects of changes in ventilation strategies over the years on the outcomes of these patients, due to insufficient data [40,41]. A better understanding of and research on brain-lung interactions, especially with a focus on understanding the exact pathophysiology of ARDS following aSAH and the interaction of high ICP with lung protective ventilation, are necessary.

The present study had several limitations. First, this study showed substantial heterogeneity ($I^2 > 90\%$) in estimating the prevalence of ARDS after aSAH, owing to the variability of the included studies, which represents the current state of limited data available on this topic. Publication bias may also exist, due to the nature of systematic reviews and meta-analyses, which could cause an overestimation of the prevalence of ARDS after aSAH. Similarly, we were unable to account for observer bias between the clinicians' interpretations of the imaging and ventilation data used for the diagnosis of ARDS. Bilateral pulmonary infiltration, from pulmonary edema due to stress cardiomyopathy, should be ruled out before ARDS is diagnosed, although none of the included articles discussed this information. The included studies also involved a wide range of study periods, and we were therefore unable to account for differences in the prevalence of ARDS due to changes in clinical practice in patients with aSAH and changes in the definition of ARDS over time. We found, however, that the prevalence of ARDS did not change between studies done before and after 2012. Additionally, only half of the studies included reported neurological outcomes, which may not accurately represent the entire population of patients with aSAH. The timing of the neurological outcome assessments also had variable follow-up times. Lastly, the assessment of risk factors for ARDS was limited by missing data on pre-specified risk factor variables, and caution needs to be taken when interpreting the data, due to heterogeneities across the studies. Despite these limitations, the present study serves as a foundation for reporting the common occurrence of ARDS, as well as its timing and outcomes in patients with aSAH.

In the present meta-analysis, approximately one in six patients developed ARDS shortly after aSAH, with a mean time of 3 days, and patients with high-grade aSAH were more likely to develop ARDS. The presence of ARDS is associated with higher mortality and worse neurologic outcomes in these patients. As such, further research on prevention and treatment strategies for aSAH-associated ARDS is warranted.

## ARTICLE INFORMATION

### Ethics statement

Not applicable.

### Conflict of interest

No potential conflict of interest relevant to this article.

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**Supplementary materials**

Supplementary materials can be found via https://doi.org/10.18700/jnc.220043.

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# Use of temperature changes and pro-inflammatory biomarkers to diagnose bacterial infections in patients with severe cerebral trauma

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ORIGINAL ARTICLE

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**Background:** In patients undergoing neurosurgeries, inflammation and infection are strongly related; however, inflammation can be present without infection. Midregional proadrenomedullin (MR-proADM) is a relatively new sepsis biomarker that is rarely used clinically. Recently, the concept of DiffTemp was introduced, that is, a >1°C rise from individual normal temperature accompanied by malaise, as a more accurate definition of temperature assessed as fever. The aim of the present study was to examine the importance of C-reactive protein (CRP), white blood cells, procalcitonin, and MR-proADM levels and DiffTemp.
**Methods:** This prospective, comparative study had a quantitative approach. Forty-two patients, aged >18 years and presenting with severe cerebral trauma were included from a neurosurgical intensive care unit. The outcome variable was infection; group 0, no infection (n=11); group 1, suspected infection (n=15); and, group 2, confirmed infection (n=16). Group assignments were performed using biomarkers, medical records, bacterial cultures, and International Classification of Diseases-10, and by the clinical assessment of criteria for nosocomial infections by a neurosurgeon.
**Results:** On comparing groups 1 and 2, MR-proADM and DiffTemp were associated with a higher risk of confirmed infection (odds ratio, 5.41 and 17.14, respectively). Additionally, DiffTemp had a 90.9% specificity in patients with no infection and a 93.8% sensitivity in patients with confirmed infections. CRP and procalcitonin levels were not associated with an increased risk of confirmed infection.
**Conclusion:** Increased levels of MR-proADM were associated with a higher risk of confirmed infection. DiffTemp was associated with a higher risk of having a confirmed infection.

**Keywords:** Infection; Fever; DiffTemp; Trauma; Body temperature; Midregional proadrenomedullin

## INTRODUCTION

Patients with severe cerebral trauma are susceptible and have a higher risk for developing infections that can be life threatening [1]. Moreover, in these patients, the length of stay (LOS) at the neurosurgical intensive care unit (NICU) and the duration between intensive care and rehabilitation are among the significant factors associated with unfavorable outcomes one year after injury [2]. A recently published multicenter study of complications after severe cerebral trauma showed that infection during the care peri-

od strongly affects the patient's condition in both the short and long terms (1 year after the injury), along with the LOS [1]. A significant clinical sign of suspected infection is increased body temperature that is assessed as fever. Approximately 70% of critically ill patients undergoing neurosurgeries develop fever, although 50% are reported to be due to non-infectious causes such as extreme physiological stress and the inhibition of thermogenesis [3]. Nevertheless, as infection is life threatening and it affects the LOS, it is of utmost importance to prevent, detect, and treat infections [1,2]. However, as tissue damage also triggers an inflammatory immune response, including increased body temperature, it might be a challenge to detect and treat ongoing infections. In the present study, we studied different factors and biomarkers, including C-reactive protein (CRP), white blood cells (WBCs), midregional proadrenomedullin (MR-proADM), and procalcitonin. These biomarkers are clinically used to help diagnose infections in patients with severe cerebral trauma.

### Body temperature and the concept of Diff Temp

Elevated body temperature is related to adverse outcomes in critically ill patients, especially in those with severe cerebral trauma. It is associated with long stays in the NICU, increased intracranial pressure, unconsciousness, poor functional status, increased excitatory amino acid release and metabolic demands, and intracerebral edema [4]. The analysis of changes in temperature, rather than the absolute values, may facilitate in reducing the time to antimicrobial therapy [5]. A large cohort study of patients in the NICU concluded that, after controlling for severity of illness, diagnosis, age, and complications, elevated body temperature was independently associated with longer NICU and hospital LOS, a higher mortality rate, and worse outcomes. The study also concluded that it remains to be determined whether the control of elevated temperature can affect these relationships [6].

The prevailing paradigms of normal body temperature as 37°C and fever as > 38°C were established in the mid-19th century by the German physician Wunderlich [6]. Notably, the measurements were performed on patients who were ill, indicating that a large number of them may have been febrile and that axillary measurements were used, which gives only an estimate of peripheral temperature [6,7]. Since then, research has shown that body temperature varies between groups, that is, gender and age [6,8-10], as well as due to temperature gradients within the body [6,9,11-14]. In addition, since 1869, the technical design of thermometers has greatly improved, especially the technical accuracy [6]. This has been confirmed by Mackowiak and Worden [15], who showed that the thermometer used by Wunderlich measured 1.4°C to 2.2°C higher than modern digital devices.

However, as the normal body temperature shows individual variation, a more logical approach is that the same should hold true for the febrile range [16-18]. We tested this hypothesis in a large multicenter study by measuring ear temperatures in 2006 apparently healthy individuals aged [2,4], and 10 to 89 years, of whom 1,700 also claimed that their temperature was assessed as fever by themselves and their children. Interestingly, the results showed that individuals reported at least 1°C increases in body temperatures from the baseline when fever occurred. Based on these results, the concept of Diff Temp was founded, that is, at least a 1°C increase from normal temperature, together with malaise, as an alternative and more accurate definition of temperature assessed as fever [10].

### Purpose/hypothesis

To study the importance of CRP, WBC, procalcitonin, and MR-pro-ADM levels and Diff Temp defined as an increase of > 1°C in individual body temperature for the early detection of ongoing infection in patients with severe cerebral trauma.

## METHODS

### Study design

The study had a prospective, comparative design with a quantitative approach.

### Sample

The inclusion criteria were as follows: patients aged > 18 years who were referred to the NICU with severe cerebral trauma and had the lowest non-sedated reaction level scale (RLS) scores from 3 to 8 in the first 24 hours after injury.

### Setting

The present study was conducted at an NICU consisting of 14 beds at a university hospital in middle Sweden that served over one million inhabitants. In March 2017, a pilot study was conducted over two weeks for feasibility. After adjusting the logistics for data collection, the study was conducted from October 2017 to April 2018. The patient, or his/her next of kin, was informed in writing and orally at admission to the NICU by the attending (RN).

The research RN at the NICU was responsible for performance and follow-up, together with the project leader (MSL). Patients aged 18 years and above with acute cerebral trauma admitted to the NICU were included. The patients were followed up multiple times daily during their stay. Based on a power of 0.80 and $P < 0.05$, the required sample size was calculated as 21 patients (7


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patients per group). However, a total of 42 patients were included, with no dropouts. Data on age, sex, and cerebral trauma diagnosis were obtained from patient medical records. Observations of vital parameters, that is, RLS score, intracranial pressure, blood pressure, pulse, breathing, pain estimation, drugs, cultures, and treatments were recorded via patient records and monitoring protocols. After the end of the care period, the course of the illness was compiled through a review of the patient's journal.

### Outcome

The study outcome was infection. After the study was performed, the main author (AT), the responsible neurosurgeon (MN), and the project leader (MSL) retrospectively reviewed the medical records for biomarkers, clinical signs and symptoms, vital parameters, intracranial pressure, International Classification of Diseases-10, and criteria for nosocomial infection. Assessments of no infection, suspected infection, and confirmed infection were then performed by the responsible neurosurgeon (MN). Most patients were administered a single dose of prophylactic antibiotics during the surgery [19,20].

Group 0: no infection (n = 11); this group consisted of patients who did not have any clinical symptoms of infection or abnormal blood levels of CRP, WBC, procalcitonin, and MR-proADM and abnormal radiographs. Group 1: suspected infection (n = 15); this group consisted of patients who had clinical symptoms of infection, such as increased oxygen demand, and/or abnormal blood levels of CRP, WBC, procalcitonin and MR-proADM, and/or abnormal radiographs. All the patients in this group had negative blood, sputum, and urine cultures and no visual signs of postoperative wound infection (swelling, redness, tenderness, and pus). Group 2: confirmed infection (n = 16); this group consisted of patients with abnormal blood levels of CRP, WBC, procalcitonin, or MR-proADM and/or abnormal radiographs and/or clinical symptoms, such as increased oxygen demand. All the patients included in this group had positive blood, sputum, or urine culture and/or visual signs of postoperative wound infection (swelling, redness, tenderness, and pus).

The average care time at the NICU where the study was performed was 3.5 days, which is comparable to other NICUs in the country. A total of 919 medical care events occurred between 2018 and 2020. While 131 medical care events having durations from 11 to 30 days had an occupancy of 42% in the NICU, 374 medical care events having durations from 1–3 days had an occupancy of only 16%. This shows how LOS is the most important factor in hospital occupancy (Fig. 1). Table 1 gives an overview of the infection diagnoses of the included patients in groups 1 and 2.

### Confounders

All the 42 patients were treated according to the NICU clinical routine without any intervention, which means that patients were administered intravenous doses of paracetamol (4,000 mg daily). Paracetamol is known to decrease the body temperature by 0.4°C [21], with an induction time of 30–60 minutes and a half-life of 1.9–2.5 hours [22]. The patients were administered 1,000 mg paracetamol four times a day, at 6 AM, 12 AM, 6 PM, and 12 PM. As paracetamol and diurnal variation are considered as confounders, the measurement point for the analysis of body temperature was decided as 6 AM to minimize the risk of its effect on body temperature. As no significant difference was found between the body temperatures measured in the right and left ears, the mea-

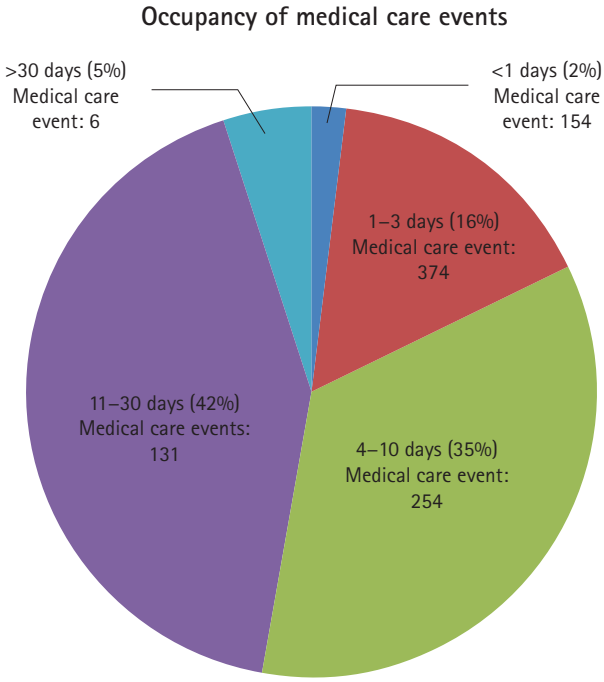


**Fig. 1.** The average care time at the neurosurgical intensive care unit where the study was performed.

**Table 1.** Descriptive statistics of diagnoses across categories of infection

| Variable | Suspected Infection (n=15) | Confirmed infection (n=16) |
|---|---|---|
| Pneumonia | 7 | 15 |
| Meningitis | 5 | 3 |
| Urosepsis | 0 | 2 |
| Central venous catheter infection | 0 | 1 |
| Unclear | 5 | 0 |

Patients in the same group can have two simultaneous diagnoses.

surement from the right ear at 6 AM was used in the statistical analysis [23].

### Measurements

*Biochemical and inflammatory markers*

To monitor biochemical markers and the inflammation status, daily blood samples were taken for the analysis of high-sensitivity CRP (hs-CRP), WBC, procalcitonin, and MR-pro-ADM levels at 5 AM in conjunction with regular sampling. The time is described in days. Time 1 refers to day one of admission to the NICU. This means that one value of each biomarker was analyzed each day during the NICU stay. The body temperature measured at 6 AM was analyzed, which means one value of body temperature was analyzed each day during the NICU stay. The samples were drawn at this specific time to avoid other confounding factors, such as medications and operations, as much as possible. All the samples, except that taken for the MR-proADM analysis, were analyzed within 24 hours at the Diagnostic Center, Östergötland County Council. The samples for MR-proADM were stored in Biobank 935 before analysis. hs-CRP levels were analyzed using the immuno-turbidimetric analysis (Roche Diagnostics, Basel, Switzerland); WBC levels, automated analysis system (Cell-Dyn Sapphire; Abbott Scandinavia AB, Stockholm, Sweden); procalcitonin levels, luminescence (Roche Diagnostics, Basel, Switzerland); and, MR-pro-ADM levels, time-resolved amplified cryptate emission (Brahms, Hennigsdorf, Germany).

### Body temperature

Using ear measurements is a routine method for assessing body temperature in the NICU. Special thermometers were provided by the research team for this study. Body temperature measurements were performed using infrared technology in both the ears (Genius 2; Medtronic, Boston, MA, US). Body temperatures were measured simultaneously from the right and the left ears every 4 hours between 6 AM and 12 PM, and when required in conjunction with a changed condition, throughout the care period. In the present study, DiffTemp was used to compare the individual morning body temperatures (6 AM) from one day to the next. All the thermometers were calibrated and set to measure the actual temperature without predetermined additions for adjustments to another measurement site (Medtronic). With respect to circadian rhythm and the intravenous administration of paracetamol, temperature measurements at 6 AM were chosen for estimating DiffTemp.

### Statistical analysis

Data were inserted into IBM SPSS ver. 27 (IBM Corp., Armonk, NY, USA) for analysis. The outcome variable was a record of infection in the patient record [23]. Data were analyzed using descriptive statistics, Shapiro-Wilk tests to determine normality, and Spearman correlation to determine the correlation between variables. Differences between groups were analyzed using the Kruskal-Wallis one-way analysis of variance (ANOVA) or one-way ANOVA. Multinomial logistic regression was performed to calculate DiffTemp. Multinomial logistic regression with a goodness-of-fit test was performed to compare it to the traditional assessment of fever ( > 38°C). The differences between the infection groups were then compared. A mixed-effects logistic regression analysis was used to analyze the parameters related to an increased risk of confirmed infection. Sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) for DiffTemp were analyzed using Crosstabs. Statistical significance was set at $P < 0.05$ [19,20].

A Shapiro-Wilk test was used to determine whether levels of MR-proADM, CRP, WBC, and procalcitonin and body temperature (ear) were normally distributed, and Spearman correlation coefficients were calculated to estimate correlations between variables included in the regression analysis. Of the included variables, only body temperature was normally distributed. WBC, CRP, MR-proADM, and procalcitonin levels were non-normally distributed, irrespective of the category of infection (no infection, suspected infection, confirmed infection). A significant weak uphill linear correlation was found between the levels of procalcitonin and CRP (spearman's rho = 0.346, $P = 0.000$), between MR-proADM and CRP (spearman's rho = 0.244, $P = 0.000$), and procalcitonin and MR- proADM (spearman's rho = 0.262, $P = 0.000$).

## RESULTS

The study included 42 patients, all of whom were acutely admitted to the NICU. Men and women had mean NICU stays of 15 days and 12 days, respectively. Of the 42 patients, 27 were ≥ 60 years old and 15 were < 60 years old; and, 48% of the patients were aged ≥ 60 years and 20% of patients aged < 60 years had confirmed infections during hospital care. Table 2 and Fig. 2 provide an overview of the distribution of included biomarkers and body temperature across the categories of infection.

### Pro-inflammatory biomarkers and body temperature

Table 3 provides an overview of the statistical differences in biomarkers and body temperature between the different groups. On


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**Table 2.** Descriptive statistics of variables across categories of infection

| Variable | Total | No Infection (n=11) | Suspected Infection (n=15) | Confirmed infection (n=16) |
|---|---|---|---|---|
| Age (yr) | 62±14 (20–88) | 62±10 | 61±17 | 65±14 |
| NICU stay (day) | 14±9 (2–43) | 10±10 | 14±10 | 17±8 |
| Sex (male:female) | 26:16 | 3:8 | 11:4 | 12:4 |
| hs-CRP (mg/L) | 73.11±75.72 | 41.90±54.02 | 82.25±81.54 | 74.09±73.80 |
| WBC ($\times 10^9$/L) | 12.56±5.94 | 10.99±3.02 | 11.22±3.41 | 14.10±7.60 |
| Procalcitonin (μg/L) | 0.55±2.79 | 0.39±0.50 | 0.28±0.34 | 0.83±4.01 |
| MR-ProADM (nmol/L) | 1.10±0.64 | 1.23±1.34[a] | 0.99±0.33 | 1.16±0.49 |
| Body temperature (°C) | 37.12±0.81 | 37.16±0.72 | 36.97±0.84 | 37.24±0.80 |

Values are presented as mean±standard deviation (range) or mean±standard deviation.
NICU, neurosurgical intensive care unit; hs-CRP, high-sensitivity C-reactive protein; WBC, white blood cell; MR-proADM, midregional proadrenomedullin.
[a]MR-proADM was high in this group due to an extreme outlier.

analyzing all the groups together, on the day of admission to the NICU, the mean baseline hs-CRP was 25 mg/L. On day 2, the levels increased more than two-fold to a mean of 68 mg/L, and it further doubled to 135 mg/L on day 4. The mean hs-CRP then steadily decreased from day 5, and continued to decrease over time. hs-CRP levels decreased to the same levels as those displayed on the first day of admission on day 19 during the NICU stay (Fig. 3).

Fig. 4 shows hs-CRP differences between the infection groups. All the three infection groups had the same hs-CRP peaks on day 4, although the hs-CRP peaks were higher in the suspected infection and confirmed infection groups than that in the no infection group. One patient in group 0 (no infection) underwent a re-operation, which explains the high hs-CRP levels in CRP 13 in the graph.

### Mixed-effects logistic regression

On comparing the groups with suspected and confirmed infections, WBC and MR-proADM levels and body temperature were related to the increased risk for confirmed infection, whereas CRP and procalcitonin levels were not. The WBC level had a 1.09% risk of confirmed infection ($P=0.002$; odds ratio (OR), 1.09; 95% confidence interval [CI], 1.036–1.166), and MR-proADM had a 5.41 risk of confirmed infection ($P=0.000$; OR, 5.41; 95% CI, 2.20–13.28).

Multinomial logistic regression of traditional assessment of body temperature vs. DiffTemp when comparing infection groups Traditional assessment of body temperature, that is, fever assessed as body temperature >38°C, did not show a significant risk relation with a higher risk of having a confirmed infection. DiffTemp, however, was associated with a 150% higher risk of having a confirmed infection ($P=0.001$; OR, 150.00; 95% CI, 8.378–2,685.505) as compared to no infection. DiffTemp was also related to a 17.14% higher risk of having a confirmed infection ($P=0.014$; OR, 17.14; 95% CI, 1.78–164.97) as compared to suspected infection. A goodness-of-fit test showed that the model fits the data well.

Fig. 5 shows that only one patient out of 10 in group 0 (no infection) had an increase of body temperature >1°C. In group 1 (suspected infection), 8 out of 15 patients had no increase, whereas 7 patients had increases of >1°C in body temperature. In group 2 (confirmed infection), 15 out of 16 patients had increases of >1°C in temperature. DiffTemp had a 90.9% specificity for classifying no infection, and a 93.8% sensitivity for classifying confirmed infection. The DiffTemp specificity in patients with suspected infection was 53.3%, and the sensitivity was 46.7%. DiffTemp had an NPV of 52.6% for no infection and 42.1% for suspected infection, and a PPV of 65.2% for confirmed infection and 30.4% for suspected infection.

## DISCUSSION

CRP is one of the most frequently used biomarkers for diagnosing an infectious process. Normal levels of CRP are defined as <10 mg/L, and <5 mg/L using a highly sensitive technique. The secretion of CRP begins within 4–6 hours of the stimulus. Elevations in serum CRP are most prominent in systemic infections caused by Gram-negative and Gram-positive bacterial infections. Chronic inflammation, surgery, trauma, burns, and other conditions can alter CRP concentrations. It is almost always supplemented by other blood tests and/or physical examination [24]. The CRP results from our study are in concordance with the results of other studies [25,26]. The CRP curve in Fig. 3 represents the CRP levels from the first day of admission. The peak on day 4 was homogenous for almost all the patients across the categories of infection, although the group without infection had a lower peak. The peak is probably explained by surgery since all the patients underwent surgeries within 2 days of admission to the

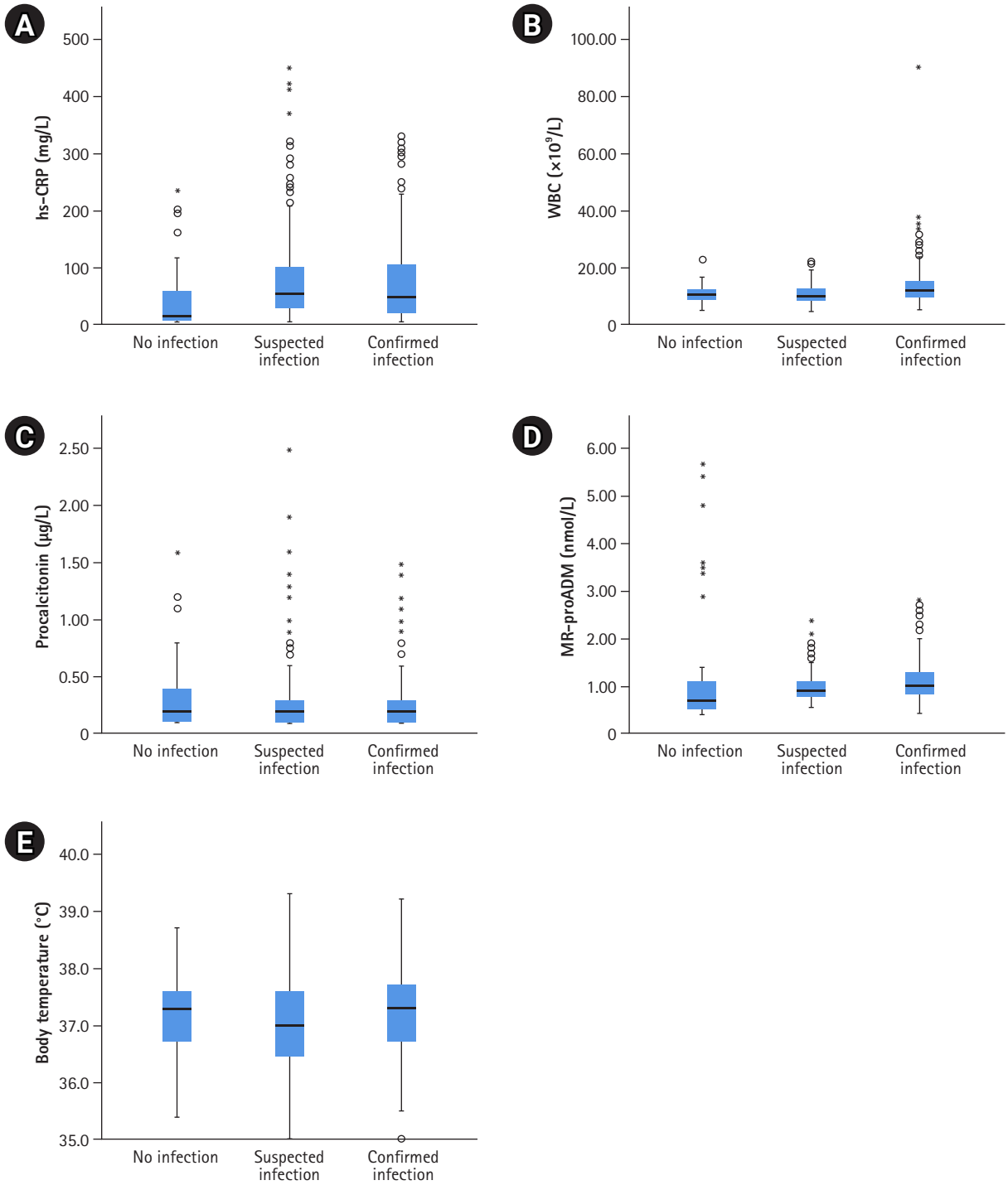


**Fig. 2.** Boxplots of (A) high-sensitivity C-reactive protein (hs-CRP), (B) white blood cell (WBC), (C) procalcitonin, (D) midregional proadrenomedullin (MR-proADM) levels, and (E) body temperature by infection group. The boxes represent the interquartile ranges (25th to 75th percentiles), the thick black line in the box is the 50th percentile (median), and the bars represent the range of results, excluding outliers. Circles are "outliers" and asterisks are "extreme outliers." No infection, n=11; suspected infection, n=15; confirmed infection, n=16. Two patients were excluded from Fig. 2C (group 2) due to extreme outliers affecting the readability of the figure. Analyzed using the independent-samples Kruskal-Wallis test.


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**Table 3.** Statistical differences between the groups

| Variable | No infection vs. suspected infection (*P*-value) | No infection vs. confirmed infection (*P*-value) | Suspected infection vs. confirmed infection (*P*-value) |
|---|---|---|---|
| hs-CRP | <0.001 | <0.001 | 0.180 |
| WBC | 0.890 | <0.001 | <0.001 |
| Procalcitonin | 0.209 | 0.769 | 0.218 |
| MR-proADM | 0.003 | <0.001 | 0.008 |
| Body temperature | 0.185 | 0.587 | 0.009 |

hs-CRP, high-sensitivity C-reactive protein; WBC, white blood cell; MR-proADM, midregional proadrenomedullin.

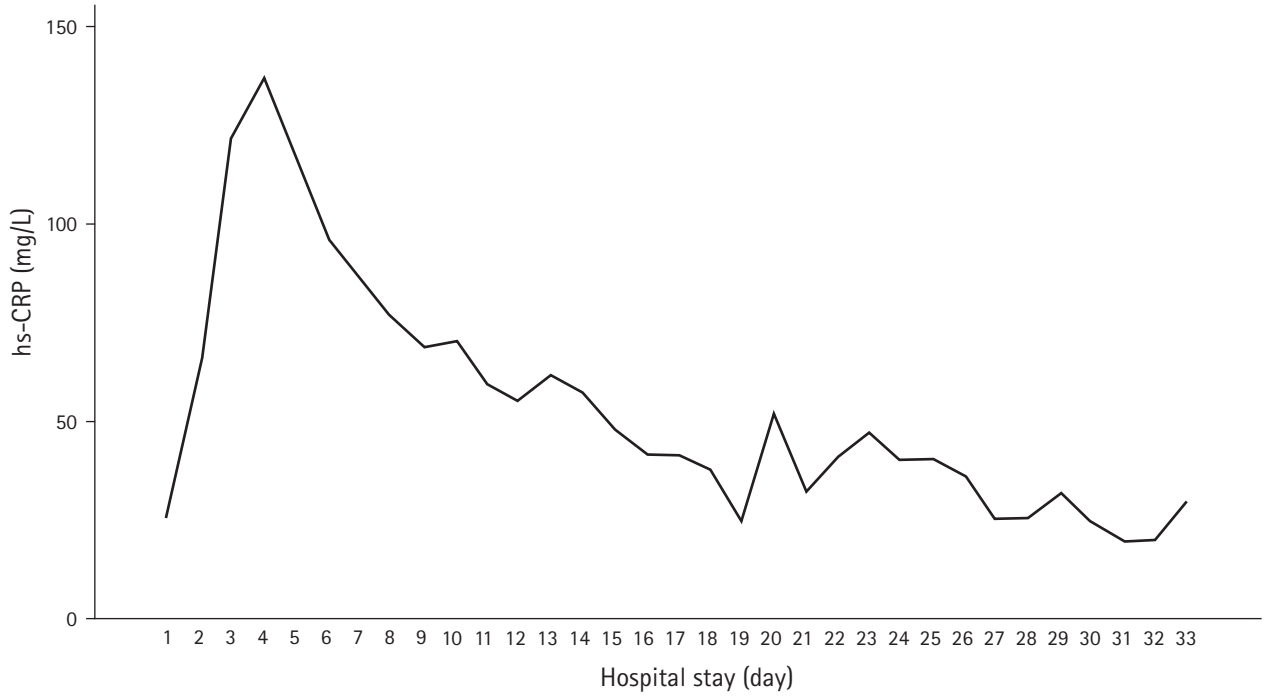


**Fig. 3.** High-sensitivity C-reactive protein (hs-CRP) levels displayed over time during hospital stay in 42 patients in the neurosurgical intensive care unit.

NICU. Another reason could be cerebral trauma, which causes inflammation and, therefore, elevated CRP levels. In addition, CRP levels started to decrease after day 5, regardless of antibiotic use or other treatments for bacterial infection, which indicates that the increased levels solely depended on surgery and cerebral trauma and not on an infectious agent. Surgery and cerebral trauma are therefore confounders for CRP levels [26,27]. This explains why a postoperative increase in CRP levels was not assessed as a sign of suspected infection by the responsible neurosurgeon in the study.

Normal variations in WBC are defined as 3.5 to 8.8 $\times 10^9$/L for individuals above the age of 16 years. Elevated WBC levels are common in bacterial infections. The WBC levels can double within hours after a stimulus, for example, a pathogen. When comparing the groups with suspected and confirmed infections, the WBC count was associated with a small risk for confirmed infection. A study by Riley and Rupert found that the WBC count is a suggestive but not a definitive marker for the presence of significant infection [28].

Procalcitonin is a precursor of calcitonin. Procalcitonin levels are low in healthy humans ( < 0.05 μg/L). The levels of procalcitonin start to increase in 4–12 hours in case of systemic infection. Procalcitonin has also been identified as a prognostic factor in sepsis [29], and it has recently become the gold standard for identifying sepsis and confirming infection [30,31]. According to Sudhir et al. [32] procalcitonin proved to be an excellent indicator of sepsis with a sensitivity of 94%. Another study by Jekarl et al. [33] concluded that procalcitonin could support and predict the unfavorable prognosis of sepsis based on third international consensus definitions for sepsis and septic shock, whereas the diag-

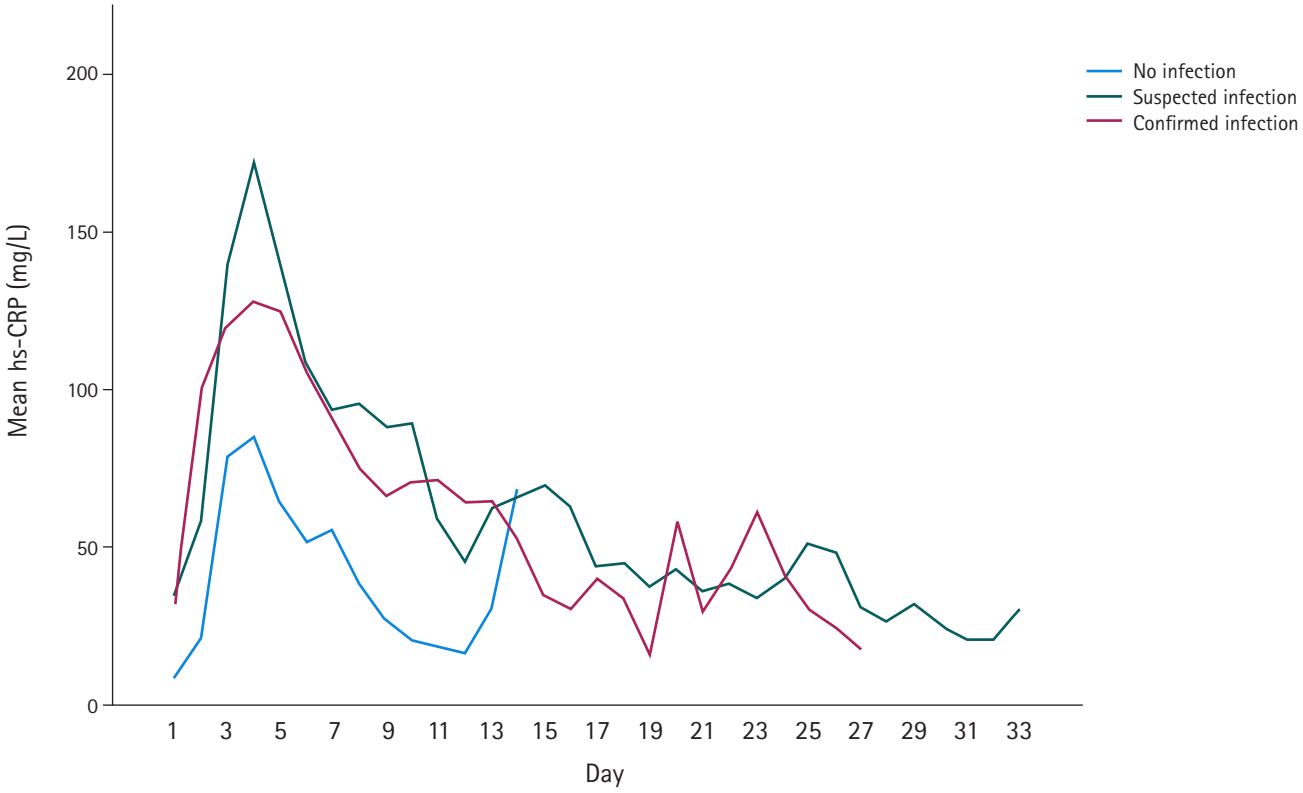


**Fig. 4.** Mean high-sensitivity C-reactive protein (hs-CRP) levels over time across the categories of infection. No infection, n=11; suspected infection, n=15; confirmed infection, n=16.

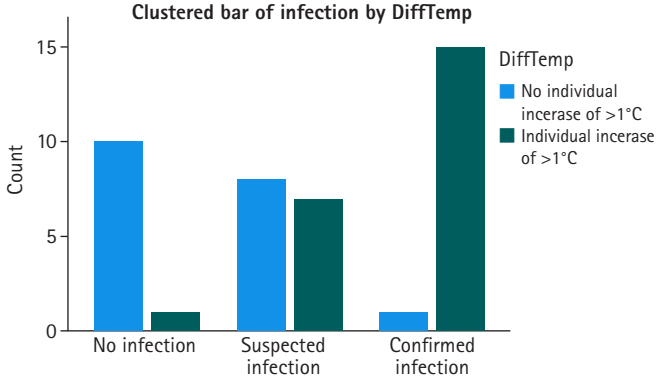


**Fig. 5.** Bar graph of the different infection groups that were organized by temperature change (defined by DiffTemp, i.e., having or not having an individual increase of >1°C) during hospital stay.

nostic potential of procalcitonin requires further evaluation. Taylor et al. [34] concluded that sepsis could be reduced using procalcitonin administration. In our present study, however, increased procalcitonin levels indicated no increased risk for infection. A study in patients with traumatic brain injury (TBI) in the NICU concluded that procalcitonin was useful for mortality prediction, but not for sepsis prediction [35]. A study by Oconnor et al. [36], which had similar settings, concluded that procalcitonin appeared to correlate with the severity of TBI and mortality. Additionally, Oconnor et al. [36] concluded that procalcitonin could not distinguish between systemic inflammatory response syndrome (SIRS) and sepsis because procalcitonin elevation correlated with the severity of injury. Sinaga et al. [37] found that procalcitonin levels are predictors of SIRS. Hence, TBI and SIRS could be confounders for procalcitonin levels, which are probable reasons for the results obtained for procalcitonin in our present study.

MR-proADM is a precursor of adrenomedullin. Adrenomedullin is acts as both a cytokine and a hormone [38]. It is suggested that it has multiple physiological functions, including being directly bactericidal [39]. Adrenomedullin also has diuretic effects, and it works as an immune-modulator and a potent vasodilator. Elevated levels of interleukin-1β and tumor necrosis factor stimulate the production of adrenomedullin [39]. MR-proADM is a marker used to diagnose and evaluate the prognosis of sepsis [40]. In the present study, we found that MR-proADM was related with a significantly increased risk for having a confirmed infection. In 2018, Önal et al. [40] identified MR-proADM as a prognostic marker that stratified the mortality risk in patients with sepsis. Önal et al. [40] also concluded that it may be helpful in the early identification and individual risk assessment of sepsis, and it may also facili-


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tate the subsequent clinical management of sepsis and septic shock.

The main and interesting findings in the present study are the promising results of using DiffTemp and MR-proADM in clinical practice. The results suggest that using MR-proADM in combination with DiffTemp could clinically help in detecting ongoing infection in patients with cerebral trauma early on and differentiate between possible and confirmed infections. This would not only help in early diagnosis and treatment, but it could also potentially help decrease the LOS and thereby reduce the financial burden. In our results, we found that the traditional assessment of body temperature with a cutoff value set to 38°C was not associated with a significant risk of having a confirmed infection on analyzing and comparing groups with suspected and confirmed infection. Using the new definition, DiffTemp showed a 17.14% higher risk of having a confirmed infection on analyzing the same two groups. This could further reinforce the hypothesis that DiffTemp is superior to traditional fever assessment. Furthermore, DiffTemp had a 90.9% specificity in patients with no infection and 93.8% sensitivity in patients with confirmed infection. Thus, DiffTemp can potentially be used to confirm infection in patients with other symptoms and/or abnormal biomarkers. It can also potentially be used to rule out infection in patients with no other symptoms and/or abnormal biomarkers. The detection of infection early on using DiffTemp could lead to decreased LOS, hospital occupancy, and complication rate from infections. Since DiffTemp is a new term, there are no previous studies with similar settings for comparison. Nevertheless, another study of patients in the NICU concluded that elevated body temperature independently contributes to the increased LOS [6], which supports our results since patients with confirmed infection had the longest LOS and 15 of 16 patients with confirmed infection had increased body temperatures according to DiffTemp.

The longest LOS across all the infection categories was found in patients with confirmed infection, followed by that of patients with suspected infections, whereas patients with no infection had the shortest LOS. It is well known that a longer LOS is associated with a higher risk of developing a nosocomial infection [41]. In the present study, we were unable to confirm whether these patients developed a nosocomial infection because of a longer LOS or if they had a longer LOS because they developed a post-surgical or nosocomial infection.

A previous study from an acute care hospital showed a correlation between higher age and nosocomial infections, and it concluded that daily infection rates were 59% in patients aged >60 years and 40% in younger patients [42]. In our present study, we found a lower infection rate, especially in younger subjects: patients aged >60 years had a 48% rate of infection (13/27), whereas patients below the age of 60 had a 20% rate (3/15). The rate difference between our study and the previous study may be due to differences in settings. The previously mentioned study included patients admitted to an acute care hospital, and our current study included patients with severe cerebral trauma admitted to the NICU. The difference could also be due to the small sample size in the present study. Taken together, the results suggest that MR-proADM and the assessment of temperature in fever as DiffTemp would enhance recovery and reduce LOS after severe brain injury by detecting ongoing infection early on. However, randomized placebo-controlled trials are needed to confirm this.

### Limitations of the study

The sample size was small, and our 42 patients and the infection groups were not equally distributed. To draw more conclusions, a larger study should be conducted. In addition, hospital stays varied widely between and within the groups of patients. However, patients were followed up during the entire hospital stay, and the number of repeated measurements over time was large in all the patients, which increased the amount of analyzed data.

In the present study, we used bacterial cultures. Patients with negative bacterial cultures but positive clinical signs and biomarkers were included in the suspected infection group. This means that some patients in this group had an inflammatory process, whereas others had an infectious process that could not be objectively identified. However, MR-proADM and DiffTemp showed promising results in distinguishing patients with suspected infection from those with confirmed infection. An advantage of the present study is that it mirrors the current clinical difficulty in confirming infectious processes and presents new methods for the guidance and investigation of infection.

### Conclusion

DiffTemp and MR-proADM were associated with an increased risk of infection in patients with severe cerebral trauma, whereas CRP and procalcitonin did not show any significantly increased risks of infection. DiffTemp is a new concept for assessing fever, which we found to be superior to the traditional predetermined fever temperature assessment (>38°C), but further studies are needed.

## ARTICLE INFORMATION

### Ethics statement

Ethical approval was granted by the Ethics Committee of the Fac-

ulty of Health Sciences, Linköping University, Sweden (2016 / 159-31). Informed consent was obtained for the handling of sensitive personal data and storage of samples in the biobank facility.

### Conflict of interest

No potential conflict of interest relevant to this article.

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The main author AT received a grant from the County Council of Östergötland for the computer documentation of the collected data. The authors declare no conflict of interest.

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### Author contributions

Conceptualization: EG, MSL, MN. Data curation: EG, MSL, MN. Formal analysis: AT, EG, MSL, NK. Funding acquisition: MSL. Methodology: NK. Project administration: MSL. Visualization: AT. Writing–original draft: AT, EG, MSL. Writing–review & editing: AT, EG, MSL, MN, NK.

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# Systolic blood pressure variability within 120 hours of admission predicts the functional outcomes at discharge of patients with acute ischemic stroke

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**Background:** Blood pressure variability (BPV) is a predictor of short- and long-term disability in patients with acute ischemic stroke (AIS). Its effect on more immediate functional outcomes has been seldom studied, and the results are inconsistent. We aimed to determine the role of BPV during the first 5 days of hospitalization in functional status at the time of discharge of patients with AIS.
**Methods:** We enrolled 134 patients diagnosed with AIS and BPV using standard deviation and coefficient of variation (CV %). These were associated with the dichotomized modified Rankin Scale at discharge using logistic regression.
**Results:** Patients with unfavorable outcomes were significantly older ($P$=0.014), had a lower body mass index ($P$=0.001), were less likely to present with dyslipidemia ($P$=0.001), had lower serum triglyceride levels ($P$=0.012), had a longer hospitalization period ($P$<0.001), and had a higher mean National Institutes of Health Stroke Scale score at admission ($P$<0.001). After adjusting for multiple confounders, the CV % of systolic blood pressure (SBP) in the first 120 hours after admission had a significant effect on functional disability at discharge.
**Conclusion:** Variability in SBP in the first 5 days of hospitalization had a deleterious effect on the functional outcomes at discharge of patients with AIS. The role of diastolic BPV seems to be significant only in the first 24 hours of admission; however, further research is required.

**Keywords:** Ischemic stroke; Treatment outcome; Blood pressure

## INTRODUCTION

Acute ischemic stroke (AIS) is the most common type of stroke and a leading cause of disability. In Europe, stroke affects approximately 1.1 million people each year and is responsible for 440,000 annual deaths [1]. Future projections predict that the number of stroke survivors will increase by 27% between 2017 and 2047 due to lower fatality rates and aging of the population [2]. Therefore, the need to predict the patient's functional outcome after stroke has become a concern for both clinicians and families as it allows optimization of treatment during hospitalization, plan for discharge destination, and assess the need for rehabilitation. Hypertension is the main modifiable risk factor for AIS [3], and its control is crucial for primary and secondary stroke prevention [4-6].

In fact, many systematic reviews and meta-analyses have associated high blood pressure levels in patients with AIS with dependency, deterioration, and death [7,8]. Regardless of the absolute systolic (SBP) and diastolic (DBP) blood pressure levels, blood pressure variability (BPV) is an independent predictor of stroke outcome [9-15]. This association is greater with SBP variability, while the prognostic significance of DBP variability remains uncertain [15]. The detrimental effect of BPV is only partially understood; however, studies show that a rapid decline in blood pressure may extend the ischemic area and the loss of viable penumbra, whereas a sudden increase in blood pressure levels disrupts the blood-brain barrier, causing cerebral edema, elevated intracranial pressure, and augmented risk of hemorrhagic transformation [13].

Most clinical trials have focused on the association of BPV within the first 24–72 hours after AIS with the functional outcome at a 3 to 6 months follow-up, but evidence of a short-term impact is scarce and conflicting. Only a few studies have shown that greater variability in SBP was associated with poor discharge outcomes after AIS [16-18], while other studies do not support this hypothesis [19]. Moreover, most study designs have measured the BPV cumulatively over time, which may alter the statistical effect of specific time intervals after admission. In this study, we aimed to determine the role of BPV during the first 5 days of hospitalization on the functional status at the time of discharge of patients with AIS.

## METHODS

### Participants and study design

This retrospective cohort study included 134 patients diagnosed with AIS between January 2020 and April 2021. We selected patients who were admitted to our Acute Stroke Unit for up to 48 hours after the onset of symptoms and were previously independent in activities of daily living. The exclusion criteria were as follows: (1) absence of complete tomographic data, blood pressure records, and modified Rankin Scale (mRS) scores; (2) death (mRS 6) or leave during hospitalization; (3) a high degree of functional impairment before the current ischemic event (mRS ≥ 3) and severe depression of consciousness (Glasgow coma scale ≤ 8); (4) presence of systemic disease with potential interference in the patient's functional status or life span: severe psychiatric disease, dementia, hepatic insufficiency, renal insufficiency, pulmonary insufficiency, and hypertensive encephalopathy. The diagnosis of AIS was based on the guidelines for diagnosis and treatment of AIS and was further confirmed using a head computerized tomography.

### Data collection and outcome definition

Demographic (age and sex) and anthropometric data (body mass index [BMI]), comorbidities (smoking and drinking history, hypertension, heart failure, diabetes, dyslipidemia, previous stroke, coronary heart disease, and atrial fibrillation), laboratory data (fasting blood glucose, total cholesterol, triglycerides, high-density lipoprotein, and low-density lipoprotein levels), and clinical data (onset-to-door and door-to-needle times) were collected at the time of admission of each patient. An National Institutes of Health Stroke Scale (NIHSS) score was determined by an experienced physician at admission. The mRS was used to assess stroke disability at discharge, and patients were dichotomized as having favorable (mRS 0–2) and unfavorable functional outcomes (mRS 3–5).

### Blood pressure monitoring and variability

Blood pressure was measured approximately three times daily (at 08:00–10:00, 13:00–15:00, and 18:00–20:00) by an experienced nurse using an automated electronic sphygmomanometer in the patient's non-paretic arm. Blood pressure was recorded thrice for each evaluation, and the mean value was registered in the electronic medical records as part of routine care. We determined SBP and DBP variability during hospitalization using the standard deviation (SD) and the coefficient of variation (CV %; 100 × SD/mean) to reduce the influence of the mean blood pressure levels on the dispersion of the data. The SD and CV % were later analyzed using mean and SD. We analyzed BPV at three different and mutually exclusive time intervals (0–24 hours, 25–72 hours, and 73–120 hours) following admission.

### Statistical analyses

Descriptive statistics included mean and SD or median and interquartile range (IQR) for continuous variables, and absolute and relative frequency for categorical variables. The distribution of the data was assessed using the Kolmogorov-Smirnov test. Group differences in functional outcomes were studied using the chi-square test, Student t-test, and Mann-Whitney test. Univariate binary logistic regression was performed to study the effect of BPV on functional outcomes at discharge using the CV % at different periods after admission. The odds ratio (OR) for an mRS score of 3 to 5 and their respective 95% confidence interval (95% CI) were calculated. The CV % significantly associated with a poor functional outcome was used for multivariate regression models adjusted for age and BMI in model 1, whereas model 2 was further adjusted for the presence of dyslipidemia, thrombectomy, and NIHSS score at admission. All statistical analyses were performed using the IBM SPSS ver. 25 (IBM Corp., Armonk, NY, USA). A

two-tailed *P*-value < 0.05 was considered statistically significant.

## RESULTS

Table 1 describes and compares the characteristics of the 134 enrolled patients between outcome groups. The mean age was 75.2 ± 12.9 years, and 71 patients (53.0%) were males. Patients had a median NIHSS score of 5.0 (IQR, 8) at admission and were discharged after a median hospital stay of 4.0 days (IQR, 6) with a median mRS score of 2.0 (IQR, 2). Based on the latter, we compared 84 patients (62.7%) with favorable functional outcomes against 50 patients (37.3%) with unfavorable outcomes at discharge. Group comparisons showed that patients with unfavorable outcomes were significantly older ($P = 0.014$), had a lower BMI ($P = 0.001$), were less likely to present with dyslipidemia ($P = 0.001$), had lower serum triglyceride levels ($P = 0.012$), had a longer hospitalization period ($P < 0.001$), and had a higher median NIHSS score at admission ($P < 0.001$). The proportion of patients who underwent thrombectomy was lower in those with unfavorable outcomes ($P < 0.001$).

**Table 1.** Characteristics of the patients with acute ischemic stroke

| Variable | Overall (n=134) | Favorable outcome (n=84) | Unfavorable outcome (n=50) | *P*-value |
|---|---|---|---|---|
| Age (yr) | 75.2±12.9 | 73.3±13.3 | 78.4±11.6 | 0.014 |
| Sex | | | | 0.211 |
| Male | 71 (53.0) | 48 (57.1) | 23 (46.0) | |
| Female | 63 (47.0) | 36 (42.9) | 27 (54.0) | |
| BMI (kg/m$^2$) | 26.6±4.9 | 27.8±5.1 | 24.6±3.9 | 0.001 |
| Comorbidity | | | | |
| Smoking | 28 (20.9) | 21 (25.0) | 7 (14.0) | 0.130 |
| Drinking | 33 (24.6) | 22 (26.2) | 11 (22.0) | 0.586 |
| Hypertension | 104 (77.6) | 65 (77.4) | 39 (78.0) | 0.934 |
| Heart failure | 38 (28.4) | 22 (26.2) | 16 (32.0) | 0.471 |
| Diabetes | 57 (42.5) | 35 (41.7) | 22 (44.0) | 0.792 |
| Dyslipidemia | 101 (75.4) | 71 (84.5) | 30 (60.0) | 0.001 |
| Previous stroke | 18 (13.4) | 10 (11.9) | 8 (16.0) | 0.501 |
| Coronary heart disease | 33 (24.6) | 24 (28.6) | 9 (18.0) | 0.170 |
| Atrial fibrillation | 48 (35.8) | 31 (36.9) | 17 (34.0) | 0.734 |
| Laboratory data (mg/dL) | | | | |
| Fasting blood glucose | 136.5±48.7 | 137.7±55.0 | 134.4±36.2 | 0.706 |
| Total cholesterol | 170.7±43.3 | 170.3±45.9 | 171.5±38.7 | 0.895 |
| Triglyceride | 117.1±53.3 | 125.0±57.8 | 102.2±40.3 | 0.012 |
| HDL cholesterol | 47.9±13.0 | 46.7±13.1 | 50.2±12.6 | 0.187 |
| LDL cholesterol | 110.0±41.6 | 109.6±43.6 | 110.6±38.1 | 0.904 |
| SBP at admission (mmHg) | 149.5±26.5 | 147.6±24.8 | 152.6±29.0 | 0.291 |
| TOAST classification | | | | 0.694 |
| Large artery atherosclerosis | 73 (54.5) | 48 (57.1) | 25 (50.0) | |
| Small vessel occlusion | 31 (23.1) | 19 (22.6) | 12 (24.0) | |
| Cardioembolism | 14 (10.4) | 8 (9.5) | 6 (12.0) | |
| Other determined etiology | 1 (0.7) | 0 | 1 (2.0) | |
| Undetermined etiology | 15 (11.2) | 9 (10.7) | 6 (12.0) | |
| Onset-to-door time (min), median (IQR) | 74.0 (285) | 60.5 (212) | 100.5 (409) | 0.069 |
| Door-to-needle time (min), median (IQR) | 51.0 (45) | 51.0 (49) | 50.5 (37) | 0.316 |
| IV tPA | 28 (20.9) | 22 (26.2) | 6 (12.0) | 0.051 |
| Thrombectomy | 15 (11.2) | 13 (15.5) | 2 (4.0) | 0.042 |
| NIHSS score at admission, median (IQR) | 5.0 (8) | 3.0 (4) | 8.5 (9) | <0.001 |
| In-hospital stay duration (day), median (IQR) | 4.0 (6) | 4.0 (3) | 7.0 (11) | <0.001 |

Values are presented as mean±standard deviation, or number (%) unless otherwise indicated.
BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; TOAST, trial of Org 10172 in acute stroke treatment; IQR, interquartile range; IV tPA, intravenous tissue-type plasminogen activator; NIHSS, National Institutes of Health Stroke Scale.


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The mean blood pressure and BPV statistics and their associations with unfavorable functional outcomes at discharge are summarized in Table 2. The average number of blood pressure records per patient was 5.5 ± 2.6 during the first 24 hours after admission, 5.8 ± 2.2 during the 25–72 hours interval, and 4.9 ± 2.1 during the 73–120 hours of hospitalization. There were no significant associations between the mean absolute blood pressure values and clinical outcomes at discharge for all time intervals. Overall, the mean CV % of both SBP and DBP was higher during the 73–120 hours period. The SBP variability showed unadjusted associations with poor functional outcomes at all intervals. However, DBP variability was associated with poor outcomes only during the first 24 hours following admission.

We created a multivariate regression model for each CV % that was significantly associated with the functional outcomes at discharge to adjust for potential confounders found in the group comparison analysis (Table 3). The SBP variability in the first 120 hours after admission increased the risk of poor functional status at discharge after adjusting for age and BMI in model 1 and for remaining confounders in model 2. The effect of DBP variability during the first 24 hours of hospitalization was also associated with a poor functional outcome at discharge, with patients exhibiting a three-fold higher risk of unfavorable outcomes at discharge (OR, 3.043; 95% CI, 1.643–5.635; $P < 0.001$) per additional unit of the CV %.

## DISCUSSION

Our data demonstrated that increased SBP variability up to 120 hours after admission is associated with a higher risk of disability at discharge when adjusting for demographic and clinical confounders. This is especially useful because it encourages tightening of blood pressure monitoring and its control during the first 5 days of hospitalization as well as weighting clinical decisions based on those readings. However, the mechanism underlying this association remains unclear. While it is true that blood pressure fluctuations contribute to tissue ischemia and lesion expansion, an inverse causality can also be hypothesized given that severe strokes lead to greater autonomic dysfunction and thus higher BPV [13], which was accounted for by correcting our regression model 2 for stroke severity.

However, BMI, serum triglyceride levels, and the prevalence of dyslipidemia were lower in patients with worse outcomes. We hypothesized that the usual body weight loss in the elderly

**Table 2.** SBP and DBP values and variability and their association with poor functional outcomes at discharge

| Time from admission | Overall | Favorable outcome | Unfavorable outcome | Unadjusted OR (95% CI) | *P*-value |
|---|---|---|---|---|---|
| 0–24 hr (741 readings) | | | | | |
| Mean SBP | 139.7±16.6 | 138.9±14.4 | 141.1±19.8 | 1.008 (0.987–1.030) | 0.458 |
| SD SBP | 14.0±5.4 | 12.1±3.6 | 17.4±6.4 | 1.242 (1.134–1.360) | <0.001 |
| CV % SBP | 10.0±3.6 | 8.7±2.4 | 12.3±4.1 | 1.425 (1.234–1.646) | <0.001 |
| Mean DBP | 76.9±10.7 | 77.2±9.5 | 76.5±12.4 | 0.994 (0.961–1.027) | 0.714 |
| SD DBP | 7.5±3.1 | 6.0±1.8 | 10.1±3.2 | 2.268 (1.684–3.054) | <0.001 |
| CV % DBP | 9.8±4.0 | 7.7±2.3 | 13.5±3.8 | 2.198 (1.667–2.898) | <0.001 |
| 25–72 hr (757 readings) | | | | | |
| Mean SBP | 130.7±16.1 | 132.0±13.3 | 128.3±20.1 | 0.985 (0.962–1.009) | 0.211 |
| SD SBP | 11.3±5.1 | 9.1±3.7 | 14.9±4.9 | 1.356 (1.216–1.512) | <0.001 |
| CV % SBP | 8.7±3.8 | 7.1±2.8 | 11.3±3.9 | 1.502 (1.295–1.743) | <0.001 |
| Mean DBP | 72.4±10.6 | 73.6±10.3 | 70.1±10.8 | 0.968 (0.934–1.003) | 0.076 |
| SD DBP | 8.0±3.8 | 7.6±4.2 | 8.5±2.9 | 1.061 (0.965–1.167) | 0.223 |
| CV % DBP | 10.9±4.7 | 10.6±5.1 | 11.5±3.9 | 1.042 (0.965–1.124) | 0.296 |
| 73–120 hr (459 readings) | | | | | |
| Mean SBP | 127.3±14.4 | 128.3±12.7 | 125.7±16.8 | 0.987 (0.958–1.017) | 0.397 |
| SD SBP | 13.4±4.5 | 11.9±4.0 | 15.8±4.1 | 1.273 (1.119–1.447) | <0.001 |
| CV % SBP | 10.5±3.4 | 9.3±3.1 | 12.6±2.8 | 1.457 (1.207–1.759) | <0.001 |
| Mean DBP | 68.9±10.0 | 69.8±9.6 | 67.2±10.6 | 0.973 (0.932–1.017) | 0.230 |
| SD DBP | 7.9±3.8 | 7.5±4.1 | 8.4±3.0 | 1.060 (0.947–1.187) | 0.308 |
| CV % DBP | 11.6±5.8 | 11.0±6.2 | 12.8±5.0 | 1.053 (0.978–1.134) | 0.169 |

Values are mean±standard deviation.
SBP, systolic blood pressure; DBP, diastolic blood pressure; OR, odds ratio; CI, confidence interval; SD, standard deviation; CV %, coefficient of variation.

**Table 3.** Multivariate logistic regression of independent predictors of an unfavorable functional outcome at discharge using blood pressure variability (CV %) during hospitalization

| BPV after admission | Model 1[a] | | Model 2[b] | |
|---|---|---|---|---|
| | OR (95% CI) | *P*-value | OR (95% CI) | *P*-value |
| CV % SBP 0–24 hr | 1.420 (1.202–1.676) | <0.001 | 1.386 (1.123–1.712) | 0.002 |
| CV % DBP 0–24 hr | 2.463 (1.677–3.618) | <0.001 | 3.043 (1.643–5.635) | <0.001 |
| CV % SBP 25–72 hr | 1.595 (1.329–1.914) | <0.001 | 1.518 (1.219–1.891) | <0.001 |
| CV % SBP 73–120 hr | 1.504 (1.207–1.874) | <0.001 | 1.352 (1.044–1.751) | 0.022 |

CV %, coefficient of variation; BPV, blood pressure variability; OR, odds ratio; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; NIHSS, National Institutes of Health Stroke Scale.
[a]Adjusted for age and body mass index; [b]Adjusted for age, body mass index, dyslipidemia, thrombectomy, and NIHSS score at admission.

might justify most of the effect by decreasing the ability of resilience during periods of health deterioration and functional recovery. Regarding serum triglyceride levels and dyslipidemia prevalence, a probable explanation might reside in the tendency to better identify comorbidities in the debilitated patient due to regular follow-up, allowing for better diet and pharmacologic control.

The mean SBP and DBP values were not associated with a higher functional impairment at discharge, although significant effects were indicated in the respective SDs and CVs. We only found unadjusted and adjusted associations of DBP variability in the first 24 hours of hospitalization, but not for the remaining periods. Studies on the short-term influence of DBP variability on the neurological outcomes of patients with AIS are inconsistent. Our results are in line with studies that uncovered that DBP variability contributes to the functional deterioration of patients with AIS [20-23], although the majority of the literature exhibit that SBP variability is a better predictor of worse neurological outcomes [11,14,15,24,25]. While a high DBP variability may impact the ventricular end-diastolic volume and the cerebral perfusion in patients with impaired cerebral blood flow autoregulation, the J-curve relationship between DBP and cardiovascular events may produce a confounding effect on stroke outcomes [26].

Nonetheless, the consistent associations between BPV and worse functional outcomes in patients with AIS found over the years should prompt interventions to optimize both absolute SBP and DBP readings as well as BPV. Current guidelines recommend a permissive hypertension of up to 220/120 mmHg to maintain cerebral perfusion and less than 185/110 mmHg in patients eligible for reperfusion therapy [27]. However, optimal patient management must be tailored individually, as lowering blood pressure levels is done at the expense of increasing BPV. Drug-class effects on interindividual variation in blood pressure may also explain the risk of stroke independent of effects on mean SBP [28], with beta-blockers and angiotensin-converting enzyme inhibitors showing a greater BPV over calcium channel blockers and thiazide diuretics [13].

This study presents several advantages. To our knowledge, this is the first study to evaluate BPV in patients with AIS beyond 24 hours after admission and its relationship with outcomes at discharge. Furthermore, we analyzed BPV as a continuous variable at different time intervals, whereas previous studies considered its cumulative effect by dividing patients into percentiles according to their blood pressure indices [10,11,14,29]. This approach may result in the loss of statistical power, and using a continuous covariate provides a better understanding of the impact of minute and gradual changes in BPV on the functional outcomes.

This study has certain limitations that are worth discussing. Patient data were uncontrolled and retrospectively collected from a single center. Although the extensive exclusion criteria have assured the quality of the data, it may have led to a small sample with a selection bias. In addition, patients were older and had more comorbidities than those in previous studies, which was accounted for in the multivariate regression models. However, we could not adjust for the type of blood pressure medications due to variability in regimens and lack of complete medical records. Therefore, randomized prospective studies are required to corroborate our findings. Nonetheless, we believe our results are useful to improve the care of patients with AIS and guide future investigations.

Variability in SBP in the first 5 days of hospitalization had a deleterious effect on the functional outcomes at discharge of patients with AIS. Our data highlighted a specific time interval for greater blood pressure monitoring and therapeutic management. The contribution of DBP variability to the functional outcomes at discharge seems to be significant only to the first 24 hours of admission; however, further research is required.


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## ARTICLE INFORMATION

### Ethics statement

The study protocol was approved by the Comissão de Ética do HDFF, EPE Ethics Committee, and patient consent was waived because it is a retrospective study.

### Conflict of interest

No potential conflict of interest relevant to this article.

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### Author contributions

Conceptualization: TP. Data curation: TP, PP, ASC, FA. Formal analysis: TP. Writing–original draft: TP, PP. Writing–review & editing: MLL, TA, AG.

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# Hypomagnesemia as a prognostic marker of ischemic stroke

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**Background:** Hypomagnesemia is associated with stroke severity and increased in-hospital mortality in patients with acute ischemic stroke. This study aimed to assess whether serum magnesium concentration could predict functional outcomes of patients with acute ischemic stroke.

**Methods:** A total of 1,006 patients with acute ischemic stroke were analyzed. A serum magnesium level <1.6 mEq/L was defined as hypomagnesemia. Poor functional outcome was defined as a 3-month modified Rankin Scale (mRS) score ≥4. Multivariate logistic regression models were used to determine the effect of hypomagnesemia on the prognosis of ischemic stroke. Furthermore, patients were grouped according to severity and type of stroke. Within each group, subgroup analyses and interaction analyses were performed to determine whether the effect of hypomagnesemia on functional outcomes was still valid under different clinical conditions.

**Results:** The adjusted odds ratio (OR) for poor 3-month mRS in patients with hypomagnesemia was 2.15 (95% confidence interval [CI], 1.16–3.98; *P*=0.015). Hypomagnesemia was significantly associated with poor 3-month functional outcomes in patients with minor stroke (Initial National Institutes of Health Stroke Scale [NIHSS] score <5: adjusted OR, 4.20; 95% CI, 1.67–10.59; *P*=0.002). A significant interaction (*P*=0.047) was also observed between hypomagnesemia and the severity of the initial NIHSS. Although there was no significant interaction (*P*=0.053), hypomagnesemia was significantly associated with poor functional outcomes in the cardioembolic stroke group (adjusted OR, 3.41; 95% CI, 1.24–9.41; *P*=0.018).

**Conclusion:** Hypomagnesemia was a strong prognostic marker of poor functional outcome in certain subgroups, especially in patients with mild stroke severity and cardioembolic stroke.

**Keywords:** Magnesium; Ischemic stroke; Hypomagnesemia

## INTRODUCTION

Magnesium plays an essential role in numerous enzymatic processes, cellular metabolism, and neuronal function [1]. Although some studies have discovered the potential of magnesium as a neuroprotective agent [2-4], human trials have not demonstrated the efficacy of intravenous (IV) magnesium administration. In the Intravenous Magnesium Efficacy in Stroke (IMAGES) trial, IV infusion did not have a statistically significant effect 12 hours after stroke onset [5]. Additionally, in the Field Administration of Stroke Therapy-Magnesium (FAST-MAG) trial, prehospital use of magnesium sulfate in acute ischemic stroke showed no improvement in disability outcomes at 90 days [6].

The effect of serum magnesium on the acute phase of ischemic stroke has also been studied. A prospective study has revealed that hypomagnesemia is associated with a higher incidence of ischemic stroke [7]. In addition, decreased serum magnesium levels at the time of admission can independently increase in-hospital mortality in patients with ischemic stroke [8]. Meanwhile, a higher serum magnesium concentration is related to a lower risk of stroke severity (National Institutes of Health Stroke Scale [NIHSS] ≥ 10) and mortality [9]. With increasing interest in the disability burden from ischemic stroke, we investigated the association between hypomagnesemia and functional outcomes expressed using the modified Rankin Scale (mRS). We also evaluated the interactions of hypomagnesemia with other risk factors, such as stroke severity, stroke type, age, and history of hypertension.

## METHODS

### Study population

This was a single-center cross-sectional study. From January 2014 to July 2017, 1,549 patients with acute ischemic stroke or transient ischemic attack (TIA) who were admitted to the Department of Neurology of Korea University Guro Hospital were enrolled. The diagnosis of ischemic stroke was made based on the patients' history, clinical manifestations, and neuroimaging results (computed tomography or magnetic resonance imaging) according to World Health Organization-defined criteria. The exclusion criteria were as follows: (1) diagnosis of TIA and (2) patients with acute ischemic stroke with previous mRS ≥ 2, excluding 282 patients from the study population. A total of 1,133 patients were included in this analysis. Furthermore, we excluded patients with missing data for the 3-month mRS, initial NIHSS score, serum magnesium concentration at admission, and additional clinical data such as body weight, height, serum triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) (flow chart of patient selection; Fig. 1). Finally, 1,006 patients were selected as the study population eligible for analysis.

### Data collection

The following baseline information was collected: demographics of the patients, vascular risk factors, stroke severity (NIHSS score), laboratory test results, and stroke-related information. The demographic data of the patients included age, sex, weight, and height. Vascular risk factors for ischemic stroke include a history of hypertension, diabetes mellitus (DM), coronary heart disease, atrial fibrillation, and current smoking status. Information on these factors was gathered through interviews with the patient or the patient's family if the patient could not communicate. Current smoking status was defined as having smoked one or more cigarettes per day in the year before the onset of stroke. The demographics data of the patients and vascular risk factors obtained from the interviews were cross-matched with hospital records and laboratory data.

A series of routine laboratory investigations, including systolic blood pressure, diastolic blood pressure, total cholesterol concentration, serum TG concentration, serum HDL-C concentration, and serum LDL-C concentration, were performed. Blood pressure was measured when the patient arrived at the hospital. Blood samples used for all laboratory tests were taken within 24 hours of admission. Laboratory tests, including serum magnesium concentration, were performed in the Department of Laboratory Medi-

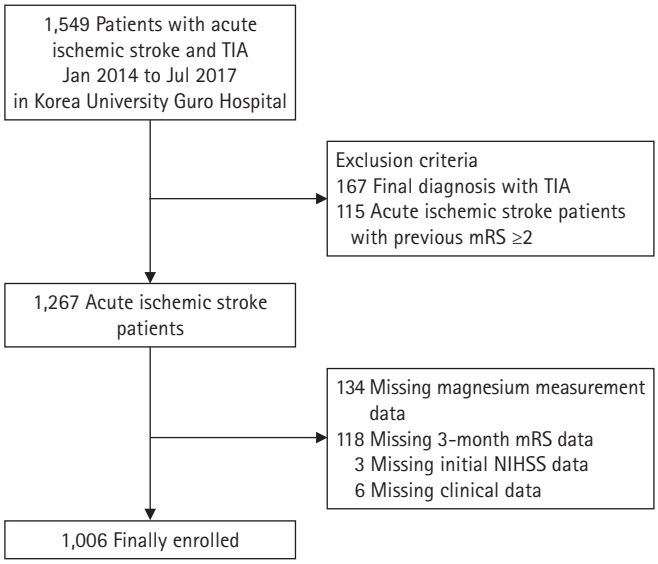


Fig. 1. Flowchart of patients' selection. TIA, transient ischemic attack; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.


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cine, Korea University Guro Hospital. Serum magnesium was measured with an atomic absorption spectrometer using the xylidyl blue reaction, according to the manufacturer's instructions, at the Department of Laboratory Medicine, Korea University Guro Hospital.

**Definitions and interpretation**

Referring to previous studies, the criterion for hypomagnesemia was defined as < 1.6 mEq/L (0.8 mmol/L) [10]. The putative cause of ischemic stroke was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification. The NIHSS score was used to describe the severity of the ischemic stroke. The initial NIHSS, defined as NIHSS, was documented by physicians as soon as the patient arrived at the emergency department before receiving specific treatment and was used for analysis. The mRS score was evaluated 3 months after discharge. The 3-month mRS was divided into two groups based on whether the patient was able to walk without assistance: good outcome (mRS < 4) and poor outcome (mRS ≥ 4) [11].

**Statistical analysis**

Baseline demographical, laboratory data, and TOAST classification of the two groups were compared according to whether the serum magnesium level is less than 1.6 mEq/L or more than 1.6 mEq/L. Continuous variables were analyzed using the independent t-test and Mann-Whitney *U*-test, whereas the frequency of categorical variables was compared using the chi-square test. To assess the effect of hypomagnesemia on poor 3-month mRS scores, a multivariable logistic regression analysis was performed. Age, hypertension, DM, history of ischemic stroke, current smoking, and total cholesterol level were included as traditional prognostic factors for ischemic stroke. Potential confounders, such as the initial NIHSS score and cardioembolic stroke, were also included according to the researcher's agreement. In addition, we performed an interaction analysis between hypomagnesemia and potential modifiers to assess whether the effect of hypomagnesemia on the 3-month mRS was affected by stroke severity (initial NIHSS score), cardioembolic stroke, age, or a history of hypertension. Subgroup analyses were performed using a multivariate-adjusted model stratified by initial NIHSS score ( < 5 vs. ≥ 5), whether the type of ischemic stroke was cardioembolic, age ( < 65 vs. ≥ 65 years), and history of hypertension. To assess unmeasured confounding effects [12] E-values were calculated for the odds ratios (ORs) of hypomagnesemia in the minor and cardioembolic stroke subgroups. All *P*-values were two-tailed with a significance level of 0.05. All statistical analyses were performed using IBM SPSS ver. 20.0 (IBM Corp., Armonk, NY, USA).

## RESULT

First, the baseline characteristics of 1,006 patients were analyzed. The mean age of the study population was 66 ± 12.9 years. Of these, 651 (64.7%) were male. The median initial NIHSS score was 3 (interquartile range, 1–6). The number of patients with poor functional outcome (3-month mRS ≥ 4) was 149 (14.8%). The baseline characteristics of the patients divided into two groups according to serum magnesium levels are presented in Table 1. The proportion of men was lower in patients with hypomagnesemia ( < 1.6 mEq/L) than in patients with higher serum magnesium levels ( ≥ 1.6 mEq/L). Patients with hypomagnesemia had significantly more conventional risk factors such as hypertension, DM, and atrial fibrillation. Regarding laboratory data, patients with hypomagnesemia had lower total cholesterol and LDL-C levels. Lastly, in the hypomagnesemia group, 27.8% of ischemic stroke cases were due to cardioembolism, while only 16.3% had a cardioembolic stroke in the other group.

Second, the effect of hypomagnesemia on the functional outcomes of ischemic stroke was estimated using univariate and multivariate logistic regression analyses (Table 2). When analyzed using a univariate logistic regression model, the odds of poor 3-month mRS were 2.29-fold higher in patients with hypomagnesemia than in those without hypomagnesemia (95% confidence interval [CI], 1.45–3.62; $P < 0.001$). With adjustment, hypomagnesemia was significantly associated with an increased risk of poor 3-month functional outcomes compared with higher serum magnesium levels (OR, 2.15; 95% CI, 1.16–3.98; $P = 0.015$). Age, hypertension, and initial NIHSS score were also significantly associated with poor 3-month mRS scores.

Third, subgroup and interaction analyses were performed to assess the effects of hypomagnesemia on functional outcomes in different clinical situations (Table 3). The patients were divided into two groups according to the independent variables mentioned above: minor (NIHSS score < 5) and moderate-severe (NIHSS score ≥ 5) stroke, age < 65 and ≥ 65 years, and presence of hypertension. Although cardioembolism was not an independently significant variable in the adjusted analysis, it was considered because patients with hypomagnesemia had more atrial fibrillation than those without hypomagnesemia [13] presumed to have a confounding relationship with serum magnesium level. In the analysis of the four groups divided by initial NIHSS and magnesium levels, the difference between the ORs of the two magnesium groups was more significant in the minor stroke group (adjusted OR, 1[ref] to 4.20) than in the moderate-severe stroke group (adjusted OR, 16.27–21.58). This is further supported by a significant interaction between hypomagnesemia and

**Table 1.** Baseline characteristics of 1,006 patients with acute ischemic stroke according to serum magnesium

| Variable | Serum magnesium <1.6 mEq/L | Serum magnesium ≥1.6 mEq/L | *P*-value |
|---|---|---|---|
| Age (yr) | 66±15 | 67±13 | 0.306 |
| Sex (male) | 64 (55.7) | 587 (65.9) | 0.031[a] |
| Hypertension | 79 (68.7) | 510 (57.2) | 0.019[a] |
| Diabetes mellitus | 60 (52.2) | 230 (25.8) | <0.001[a] |
| History of ischemic stroke | 11 (11.2) | 87 (9.8) | 0.946 |
| History of atrial fibrillation | 31 (27.0) | 152 (17.1) | 0.010[a] |
| Current smoker | 28 (24.3) | 276 (31.0) | 0.145 |
| SBP (mmHg) | 147±29 | 150±28 | 0.365 |
| DBP (mmHg) | 86±14 | 87±16 | 0.311 |
| Total cholesterol (mg/dL) | 164 (141–200) | 186 (158–215) | <0.00[a] |
| TG (mg/dL) | 101 (78–157) | 110 (78–158) | 0.893 |
| HDL-C (mg/dL) | 42 (35–50) | 42 (35–50) | 0.396 |
| LDL-C (mg/dL) | 91 (72–123) | 111 (88–134) | <0.001[a] |
| Initial NIHSS | 3 (1–7) | 3 (1–6) | 0.334 |
| TOAST classification | | | 0.019[a] |
| Large artery atherosclerosis | 34 (29.6) | 297 (33.3) | |
| Cardioembolism | 32 (27.8) | 145 (16.3) | |
| Small vessel occlusion | 18 (15.7) | 221 (24.8) | |
| Others | 5 (4.3) | 37 (4.2) | |
| Undetermined | 26 (22.6) | 191 (21.4) | |

Values are presented as mean±standard deviation, number (%), or median (interquartile range).
SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of Org 10172 in Acute Stroke Treatment.
[a]Indicates a *P*-value of <0.05.

**Table 2.** Crude and adjusted ORs of poor 3-month mRS using univariate and multiple logistic regression analyses

| Variable | Crude OR (95% CI) | *P*-value | Adjusted OR (95% CI) | *P*-value |
|---|---|---|---|---|
| Hypomagnesemia (serum magnesium <1.6 mEq/L) | 2.29 (1.45–3.62) | <0.001 | 2.15 (1.16–3.98) | 0.015[a] |
| Age (yr) | 1.08 (1.06–1.10) | <0.001 | 1.07 (1.04–1.09) | <0.001[a] |
| Sex (male) | 0.81 (0.56–1.15) | 0.234 | 1.42 (0.85–2.39) | 0.180 |
| Hypertension (yes) | 2.14 (1.45–3.15) | <0.001 | 1.95 (1.17–3.26) | 0.011[a] |
| Diabetes mellitus (yes) | 1.30 (0.90–1.88) | 0.168 | 1.18 (0.72–1.93) | 0.507 |
| History of ischemic stroke (yes) | 1.55 (0.92–2.62) | 0.103 | 0.98 (0.49–1.94) | 0.942 |
| Current smoker (yes) | 0.64 (0.43–0.97) | 0.034 | 1.25 (0.70–2.22) | 0.447 |
| 10-Unit increment in total cholesterol (mg/dL) | 0.94 (0.9–0.99) | 0.009 | 1.02 (0.95–1.06) | 0.955 |
| Initial NIHSS | 1.31 (1.26–1.36) | <0.001 | 1.32 (1.26–1.38) | <0.001[a] |
| Cardioembolism (TOAST) | 3.14 (2.13–4.62) | <0.001 | 0.83 (0.47–1.49) | 0.534 |

OR, odds ratio; mRS, modified Rankin Scale; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of Org 10172 in Acute Stroke Treatment.
[a]Indicates a *P*-value of <0.05.

the severity of the initial NIHSS score ($P = 0.047$). The E-value of the minor stroke/hypomagnesemia group was 7.87 for the point estimate and 2.73 for the CI. Similarly, hypomagnesemia was significantly associated with poor functional outcome only in the cardioembolic stroke group (adjusted OR, 3.41; 95% CI, 1.24–9.41; $P = 0.018$). The E-value was 6.28 for the point estimate and 1.79 for the CI. The interaction analysis between hypomagnesemia and cardioembolism showed a tendency toward significance ($P = 0.053$). Furthermore, the association between hypomagnesemia and poor 3-month mRS was significant in patients with a history of hypertension (adjusted OR, 4.42; 95% CI, 1.99–9.80; $P < 0.001$) and in older patients (≥65 years) (adjusted OR, 8.11; 95% CI, 3.38–19.48; $P \leq 0.001$).


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**Table 3.** The adjusted OR of poor 3-month mRS for hypomagnesemia: subgroup analysis and interactive analysis

| Variable | Serum magnesium ≥1.6mEq/L | | Serum magnesium <1.6 mEq/L | | *P*-value of interaction term |
|---|---|---|---|---|---|
| | Adjusted OR (95% CI) | *P*-value | Adjusted OR (95% CI) | *P*-value | |
| Initial NIHSS (dichotomized) | | | | | 0.047[a] |
| Minor (<5) | 1 (Ref) | | 4.20 (1.67–10.59) | 0.002 | |
| Moderate-severe (≥5) | 16.27 (9.39–28.19) | <0.001 | 21.58 (9.68–48.15) | <0.001 | |
| Cardioembolism (TOAST) | | | | | 0.053 |
| No | 1 (Ref) | | 1.44 (0.67–3.10) | 0.357 | |
| Yes | 0.62 (0.32–1.21) | 0.161 | 3.41 (1.24–9.41) | 0.018 | |
| Hypertension | | | | | 0.461 |
| No | 1 (Ref) | | 1.37 (0.35–5.37) | 0.651 | |
| Yes | 1.82 (1.06–3.13) | 0.031 | 4.42 (1.99–9.80) | <0.001 | |
| Age (dichotomized) | | | | | 0.753[b] |
| <65 yr | 1 (Ref) | | 2.68 (0.78–8.97) | 0.120 | |
| ≥65 yr | 3.84 (2.03–7.26) | <0.001 | 8.11 (3.38–19.48) | <0.001 | |

In all analyses, the same variables in Table 2 were included in the adjustment except for the stratification variable.
OR, odds ratio; mRS, modified Rankin Scale; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of Org 10172 in Acute Stroke Treatment.
[a]Interaction between hypomagnesemia and severity of the initial NIHSS score dichotomized into minor (<5) and moderate-severe (≥5); [b]Interaction between hypomagnesemia and age group dichotomized into <65 and ≥65 years.

## DISCUSSION

In our study, hypomagnesemia was associated with a higher risk of poor 3-month mRS scores, suggesting the role of magnesium as a prognostic marker in acute ischemic stroke. Furthermore, hypomagnesemia showed a stronger relationship with poor functional outcomes in certain subgroups of ischemic stroke, especially mild stroke and cardioembolic stroke.

In moderate-to-severe stroke, the initial severity of the stroke is estimated to have a major contribution to the outcome [14]. However, in minor stroke, clinical situations, such as early neurological deterioration, are related to the outcome [15], and together with other risk factors, the serum magnesium level could affect the course of the disease through several physiological actions. Hypomagnesemia deteriorates endothelial stability by inducing oxidative stress and promoting an inflammatory response [16]. Moreover, in a study of coronary artery disease, hypomagnesemia was shown to increase thrombus formation [17]. In addition, magnesium is involved in local blood pressure regulation by inducing vasodilatation [18]. In this context, hypomagnesemia could aggravate the ischemic lesion itself and perhaps the collateral circulation, thus contributing to neurological deterioration in patients with minor stroke.

Among the subtypes of ischemic stroke, cardioembolic cerebral infarction has a poor prognosis [19-21]. Our results showed that patients with cardioembolic stroke, particularly those with low serum magnesium levels, had worse outcomes. Although the effect of serum magnesium concentration on the prognosis of cardioembolic stroke has not been fully established, its effects on cardiac function have been well studied [13]. As an essential cofactor for the Na-K ATP pump, magnesium is involved in the transport of sodium and potassium across the cell membrane [22]. Dysfunction of this pump in a low magnesium environment can disturb the regulation of myocardial excitability. A previous study showed that low magnesium concentration could increase sinus node automaticity [23]. Hypomagnesemia can also increase the dose required to control the rate of atrial fibrillation [24]. Since hypomagnesemia induces and exacerbates atrial fibrillation, it can also increase the frequency of early recurrent embolization, which is one of the most important factors that worsen cardioembolic stroke [25]. According to a recent study, hypomagnesemia also negatively influences ischemic lesions in the acute stage. In this study for patients who received IV thrombolytic therapy, patients with hemorrhagic transformation (HT) have significantly lower serum magnesium levels than those without HT [26]. Since HT is inherently more frequent in cardioembolic stroke, concomitant hypomagnesemia worsens the prognosis.

This study had some limitations. First, as this was an observational cross-sectional retrospective study, a causal relationship between hypomagnesemia and a poor prognosis of ischemic stroke could not be established. The study population was selected based on inclusion criteria during recruitment, and follow-up of patients after discharge was carried out thoroughly. Second, this study was conducted in a single center. Therefore, multiple cen-

ter-based studies are needed to confirm the association between hypomagnesemia and functional outcome of ischemic stroke in the general population.

Our study demonstrates the diagnostic utility of hypomagnesemia in predicting poor functional outcomes in patients with acute ischemic stroke. In addition, the results were particularly pronounced in specific patient groups, such as those with minor and cardioembolic strokes. In future studies with magnesium as a neuroprotective agent, it may be necessary to design a more specific patient population.

## ARTICLE INFORMATION

### Ethics statement

The study protocol was approved by the Institutional Review Board of the Korea University Medical Center, Guro Hospital (IRB No. 2011GR0218). The requirement of informed consent was waived.

### Conflict of interest

No potential conflict of interest relevant to this article.

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Conceptualization: SYA, CKK. Data curation: DWL, SHK, HR. Formal analysis: HR, CKK, DWL, SHK. Methodology: CKK, SYA, HR. Project administration: KMO. Visualization: SHK, DWL, JHH. Writing–original draft: HR, CKK, SYA. Writing–review & editing: HJK, JHH, CKK, KMO.

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# Takotsubo syndrome and myasthenic crisis after radiocontrast media-induced anaphylaxis: a case report

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CASE REPORT

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**Background:** Takotsubo syndrome and myasthenic crisis can be triggered by physical stress. We present the case of a woman who developed Takotsubo syndrome and myasthenic crisis following radiocontrast media-induced anaphylaxis.
**Case Report:** A 39-year-old woman presented with diplopia and ptosis. After chest computed tomography scan, her consciousness was stupor and her oxygen saturation decreased. Electrocardiography showed ST elevation, and cardiac enzyme levels increased. Echocardiography revealed severe left ventricular dysfunction. Myasthenia gravis was diagnosed based on anti-acetylcholine receptor antibody and repetitive nerve stimulation test. Extubation failed, and her weakness worsened. Her neurological condition gradually improved after steroid therapy. Repeat echocardiography demonstrated complete recovery of left ventricular dysfunction.
**Conclusion:** Takotsubo syndrome can be triggered by anaphylaxis and can occur in patients with neurological disorders; therefore, neurologists need to know about this disorder. The combination of Takotsubo syndrome and myasthenic crisis is rare but may be associated with a poor prognosis.

**Keywords:** Takotsubo cardiomyopathy; Anaphylaxis; Contrast media; Myasthenia gravis; Case report

## INTRODUCTION

Takotsubo syndrome is characterized by transient and reversible left ventricular (LV) dysfunction and is typically triggered by emotional or physical stress [1]. Myasthenic crisis can also be associated with emotional or physical stress [2]. A small number of cases have been reported describing a combination of Takotsubo syndrome and myasthenic crisis. We present the case of a woman with myasthenia gravis who developed Takotsubo syndrome and myasthenic crisis following radiocontrast media-induced anaphylaxis.

## CASE REPORT

A 39-year-old woman presented with diplopia and ptosis that worsened in the evening. She had dysarthria, dysphagia, mastication difficulty, limb and neck weakness, and mild dyspnea that had progressed for 3 weeks. She had no history of major

illness and was not taking any medications. She had no allergies to any medicines, food, or environmental allergens. Neurological examination revealed bilateral ptosis with fatigability and bilateral medial gaze limitation. The muscle powers of the limbs were Medical Research Council (MRC) grade 4/5. The strengths of neck flexion and extension were MRC grade 4/5 and MRC grade 3/5, respectively. The sensory function was normal, deep tendon reflex was normoactive, and no pathological reflexes were observed. On admission, her vital signs and routine blood investigations were normal. A 12-lead electrocardiogram (ECG) revealed normal findings with normal sinus rhythm (Fig. 1A).

After a computed tomography (CT) scan of the chest, she complained of chest tightness while being transferred to a wheelchair and suddenly lost consciousness. Her consciousness was stupor, and her oxygen saturation decreased to 80%. After manual resuscitation with a bag valve mask, she could obey simple commands but again lost consciousness. An arterial blood gas showed respiratory acidosis with hypercapnia (PH, 7.139; $PCO_2$, 77.5 mmHg; $PO_2$, 74.2 mmHg; and $HCO_3$, 26.3 mmol/L). Epinephrine 0.3 mg was injected intramuscularly, and intubation was performed. ECG showed ST elevation in lead I, II, aVL, and V2–5 (Fig. 1B); however, it was incompatible with the coronary artery territory. Creatine kinases-myocardial band (CK-MB) was 1.8 ng/mL (normal < 5.0 ng/mL) and troponin I was 0.008 ng/mL (normal < 0.047 ng/mL). She was mechanically ventilated and transferred to the intensive care unit. Sedatives with midazolam and remifentanil and inotropic with norepinephrine were infused. Intravenous heparin and dual antiplatelet therapy were initiated.

On the next day, transthoracic echocardiography (TTE) demonstrated severe global hypokinesia of the LV base, akinesia of the mid-LV to the apex without thinning, and reduced LV systolic function with LV ejection fraction of 38% (Fig. 2A). Serial ECG revealed dynamic changes with marked T-wave inversion and prolonged corrected QT interval (QTc) interval, peaking at 612 ms (Fig. 1C). CK-MB and troponin I levels were elevated, peaking at 10.9 ng/mL and 4.65 ng/mL, respectively. She did not undergo cardiac catheterization because she experienced anaphylaxis after exposure to radiocontrast media.

A diagnosis of myasthenia gravis was made based on clinical signs, positive ice pack test, elevated anti-acetylcholine receptor antibody titer (17.80 nmol/L) and significant decrement on repetitive nerve stimulation test with low frequency rates (41.5% in orbicularis oculi, 71.3% in nasalis, 27.2% in abductor digiti minimi, 50.9% in flexor carpi ulnaris, and 73.8% in trapezius). Chest CT showed about 3.3-cm sized lobulated mass at the anterior mediastinum.

Extubation failed, and her weakness worsened. The myasthenic crisis was diagnosed as superimposed on Takotsubo syndrome. High-dose intravenous methylprednisolone pulse therapy was started on day 3 of hospitalization, and prednisolone (1 mg/kg/day) was administered after methylprednisolone pulse therapy. Her neurological condition gradually improved; she was weaned off the ventilator and extubated on day 15 of hospitalization. Repeat TTE 6 and 13 days after the initial TTE demonstrated an improved LV ejection fraction of 45% and 55%, respectively (Fig. 2B). The patient was discharged on day 32 of hospitalization.

## DISCUSSION

Takotsubo syndrome, also known as Takotsubo cardiomyopathy, stress-induced cardiomyopathy, broken heart syndrome, or apical ballooning syndrome, is characterized by transient and reversible LV dysfunction. Takotsubo syndrome is typically triggered by emotional or physical stress, although approximately one-third of patients present with no identifiable stressful triggers. Takotsubo syndrome is similar to acute coronary syndrome in terms of symptoms at presentation, ECG abnormalities, elevated cardiac biomarkers, and comparable in-hospital mortality [1]. The most common symptoms of Takotsubo syndrome are chest pain, dyspnea, or syncope. ECG abnormalities in Takotsubo syndrome include ST- segment elevation, ST-segment depression, symmetric T-wave inversion, and QTc prolongation. Cardiac troponin T and CK-MB levels are elevated in most patients with Takotsubo syndrome, but the biomarkers rise only slightly compared to the extensive wall motion abnormalities in the early stages. LV regional wall motion abnormalities extend beyond the distribution of a single epicardial coronary artery, and no significant obstructive coronary artery disease that can explain the extent of LV dysfunction has been found. Although echocardiography is the first-line imaging tool for patients with suspected Takotsubo syndrome, coronary angiography plays a crucial role in ruling out alternative diagnoses, and ventriculography may show a variety of LV regional wall motion abnormalities [1,3]. Takotsubo syndrome is thought to have a benign course, but recent studies have shown that major short-term complications, such as cardiogenic shock and mortality, are comparable to those of acute coronary syndrome. LV dysfunction in Takotsubo syndrome usually resolves spontaneously within days or weeks [3]. This patient did not undergo cardiac catheterization, but was diagnosed with Takotsubo syndrome due to typical disease features. ECG showed ST elevations that were not compatible with

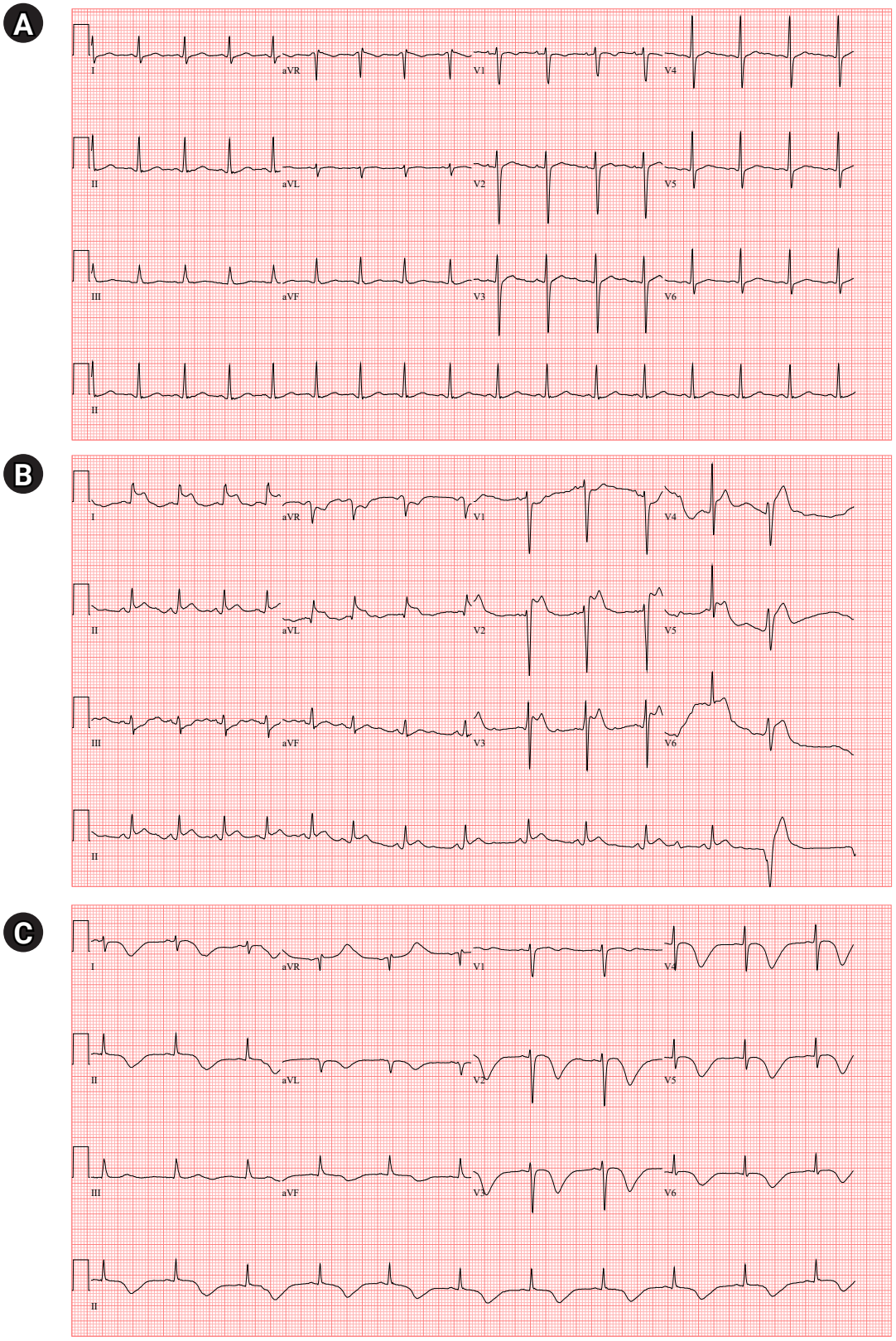


**Fig. 1.** Serial electrocardiogram (ECG). (A) ECG before anaphylaxis revealed normal findings with normal sinus rhythm. (B) ECG immediately after anaphylaxis showed ST elevation in lead I, II, aVL, and V2-5. (C) ECG on day 3 of hospitalization showed dynamic changes with marked T-wave inversion and prolonged QTc interval. aVR, augmented vector right; aVL, augmented vector left; aVF, augmented vector foot; QTc, corrected QT interval.


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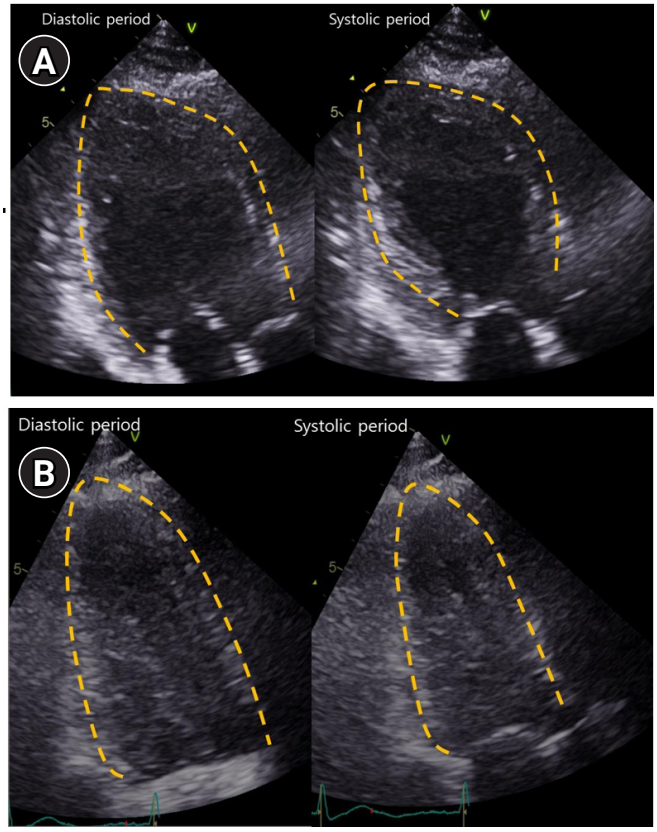


**Fig. 2.** Serial transthoracic echocardiography (TTE). (A) TTE demonstrated severe global hypokinesia of left ventricular (LV) base, akinesia of mid-LV to apex without thinning, and reduced LV systolic function. (B) Repeat TTE showed complete recovery of LV dysfunction.

coronary artery territory, echocardiography showed LV regional wall motion abnormalities that extended beyond the distribution of a single epicardial coronary artery and the appearance of apical ballooning, and CK-MB and troponin T were only slightly elevated compared to extensive wall motion abnormalities. Most importantly, LV dysfunction resolved spontaneously within 2 weeks.

In anaphylaxis, the heart, and especially the coronary arteries, are the primary targets of inflammatory mediators [4]. Cases of Takotsubo syndrome triggered by anaphylaxis have been reported [5,6]. Elevated catecholamines and excessive activation of cardiac catecholamine receptors in the left ventricle play a major role in the pathophysiology of Takotsubo syndrome. In anaphylaxis, catecholamines are released by the renin-angiotensin-aldosterone system and histamine, and catecholamines administered as treatment for anaphylaxis would also increase plasma catecholamine levels [7]. In this patient, Takotsubo syndrome was likely triggered by the critical physiological state from the anaphylaxis and subsequent administration of exogenous catecholamine (0.3 mg intravenous epinephrine).

According to the World Allergy Organization, the diagnostic criteria for anaphylaxis are (1) typical skin symptoms and significant symptoms from at least one other organ system, or (2) exposure to a known or probable allergen for that patient, with respiratory and/or cardiovascular compromise. The most frequent anaphylaxis elicitors are food, insect venom, and drugs. Other elicitor groups include natural rubber latex, seminal fluid, radiocontrast media, and medical dyes [8]. The diagnosis of anaphylaxis in this patient was made by chest tightness, dyspnea, and hypoxemia that occurred suddenly after exposure to radiocontrast media within minutes. Myasthenic crisis is a complication of myasthenia gravis, characterized by worsening muscle weakness and respiratory failure. Patients with myasthenic crises typically experience increased generalized weakness as a warning. Since this patient showed respiratory compromise that occurred suddenly after a CT scan, it appears that she had respiratory failure due to anaphylaxis, not a myasthenic crisis.

Myasthenic crisis is often triggered by stressors, such as infection, surgery, pregnancy, childbirth, or various medications. Other antecedent factors include exposure to temperature extremes, pain, sleep deprivation, and physical or emotional stress [2]. The next day after anaphylaxis, extubation failed and her weakness worsened. Myasthenic crisis was thought to be superimposed on Takotsubo syndrome. A small number of cases have been reported describing a combination of these two diseases, all of which are Takotsubo syndrome associated with myasthenic crisis [9,10]. Takotsubo syndrome following myasthenic crisis had a 15-fold higher prevalence, nearly two-fold higher all-cause mortality, and higher resource utilization than Takotsubo syndrome caused by other etiologies [10]. According to the international consensus guidelines for the management of myasthenia gravis, older reports of iodinated radiocontrast agents document increased myasthenia gravis weakness, but modern radiocontrast agents appear to be safer. It is recommended to use them cautiously and observe worsening [11]. The use of modern, low-osmolality agents has been reported with conflicting results with respect to worsening myasthenic symptoms [12,13]. The triggers of myasthenic crisis in these patients could be complex with the physical stress of anaphylaxis and Takotsubo syndrome, emotional stress from a serious physical condition, and radiocontrast agents.

Kounis syndrome, also known as allergic angina, allergic myocardial infarction, or coronary hypersensitivity disorder, is defined as the concurrence of acute coronary syndromes with conditions associated with mast cell and platelet activation. Car-

diac symptoms and signs, ECG, and laboratory findings were similar in Takotsubo syndrome and Kounis syndrome. Complete resolution of LV dysfunction within a few weeks is also characteristic of both syndromes [14]. Indeed, both syndromes can be induced by anaphylaxis. Kounis syndrome can be induced by an allergy, hypersensitivity, or anaphylaxis, and cases of Takotsubo syndrome triggered by anaphylaxis have been reported [5,6]. In addition, it is noteworthy that Takotsubo syndrome can coexist with or follow Kounis syndrome [15]. Differential diagnosis of Takotsubo syndrome or Kounis syndrome in this patient can be challenging, and the possibility that Takotsubo syndrome develops after Kounis syndrome due to anaphylaxis cannot be excluded. We report this case as Takotsubo syndrome after anaphylaxis because it is a widely recognized and well-established disease, but Kounis syndrome has been established by a limited research group and only a small number of cases have been reported.

In summary, we report a case of myasthenia gravis that developed Takotsubo syndrome and myasthenic crisis following radiocontrast media-induced anaphylaxis. Takotsubo syndrome can occur in patients with neurological disorders; therefore, neurologists need to know about this disorder. The combination of Takotsubo syndrome and myasthenic crisis is rare, but may be associated with a poor prognosis. It is unclear whether the worsening of myasthenic symptoms is related to the use of radiocontrast agents, but caution is recommended for use in patients with myasthenia gravis.

## ARTICLE INFORMATION

### Ethics statement

This study was approved by the Institutional Review Board of the National Health Insurance Service Ilsan Hospital (IRB No. NHIMC 2021-10-024). The requirement for informed consent was waived because this study is a case report of a single patient (no more than three patients) and did not include protected health information and personally identifiable information.

### Conflict of interest

No potential conflict of interest relevant to this article.

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Conceptualization: JHC, HK. Data curation: JHC, JY. Formal analysis: JHC. Writing–original draft: JHC. Writing–review & editing: all authors.

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# Utility of transoral and transcranial ultrasonography in the diagnosis of internal carotid dissection: a case report

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CASE REPORT

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**Background:** Internal carotid artery (ICA) dissection is one of the most common causes of stroke in young patients. Ultrasonographic assessment of the carotid artery is the method of choice for early detection. The use of the conventional technique for diagnosis is limited since dissection frequently occurs in the distal portion of the ICA.
**Case Report:** We describe the case of a 48-year-old Argentinian woman with malignant cerebral infarction secondary to ICA dissection. We diagnosed her with neck vessels using conventional ultrasonography and a transoral ultrasonographic approach combined with transcranial ultrasonography.
**Conclusion:** We recommend the transoral assessment of ICA combined with ultrasonography as a noninvasive method for the diagnosis of ICA dissection.

**Keywords:** Internal carotid artery dissection; Ultrasonography; Stroke

## INTRODUCTION

Internal carotid artery (ICA) dissection is one of the most common causes of stroke in young patients. Approximately 70% of affected patients are under 50 years of age, and the annual incidence is 2.6–2.9 cases per 100,000 [1,2]. Ultrasonography (US) is the method of choice for the initial assessment of ICA dissection given its safety, rapid availability, and prompt bedside use. When dissection occurs in the distal portion of the ICA, it becomes difficult to detect, and it can be evaluated indirectly through its flow characteristics in Doppler mode. Transoral ultrasonographic evaluation of the ICA is a novel technique that allows the assessment of the distal portion of the vessel. The combination of transcranial Doppler US and evaluation of intracranial vessels can be useful for the diagnosis of ICA dissection. We present a case in which conventional and transoral ICA US was used in combination with transcranial Doppler to diagnose ICA dissection.

## CASE REPORT

A 48 year-old Argentinian woman with no relevant clinical history presented to a peripheral hospital with right brachiocrural paralysis and central facial palsy. Prior to symptom onset, she underwent a neck massage for a headache and experienced initial improvement. Subsequently, she developed transient blurred vision in the

right eye and right arm paresthesia that evolved with sudden brachiocrural paralysis and facial palsy. On physical examination, she was found to have central facial palsy, right brachial plegia and anesthesia, right crural severe paresis, and mild dysarthria with an National Institutes of Health Stroke Scale score of 19. Given that head computed tomography (CT) performed on admission revealed no bleeding, she received intravenous thrombolytic therapy and was transferred to a third level private hospital.

She was admitted to the intensive care unit on arrival. Head CT showed mild hypodensity in the region of the left middle cerebral artery, and neck vessel vessels US was performed using a linear and phased array probe. There was no alteration in the proximal portion of the left ICA in the two-dimentional mode. However, pulsed wave Doppler revealed a high-resistance flow pattern compatible with distal stenosis (Fig. 1). Because it is impossible to evaluate the distal portion of the ICA, we inserted an endocavitary probe covered with a sterile sheath through the mouth and placed it on the posterior wall of the pharynx. This approach allowed visualization of the distal portion of the ICA. In the color Doppler mode, we observed a homogeneous hypoechoic image with an absence of Doppler signal adjacent to a false lumen thrombosis associated with tuning of the true lumen with low-flow velocities (Figs. 2 and 3). Subsequently, transcranial US was performed. We identified the anterior (ACA), middle (MCA), and posterior cerebral artery in color Doppler mode, and less signal was present in the left MCA. Pulsed wave Doppler revealed increased velocities compatible with significant stenosis at the proximal portions of the MCA and ACA that were associated with a postobstructive flow pattern in the distal portion of the MCA (Figs. 4-7).

Transorbital US identified the intracranial portion of the ICA in

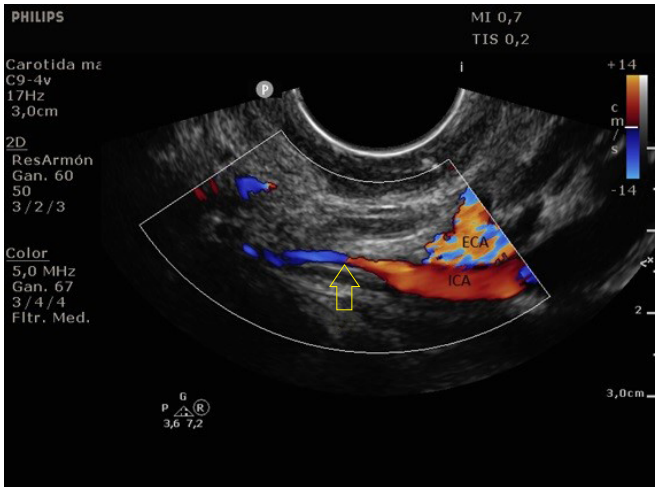


**Fig. 2.** Transoral ultrasonography. Yellow arrow; homogeneous hypoechoic image with absence of Doppler signal compatible with false lumen thrombosis and refinement of the true lumen.

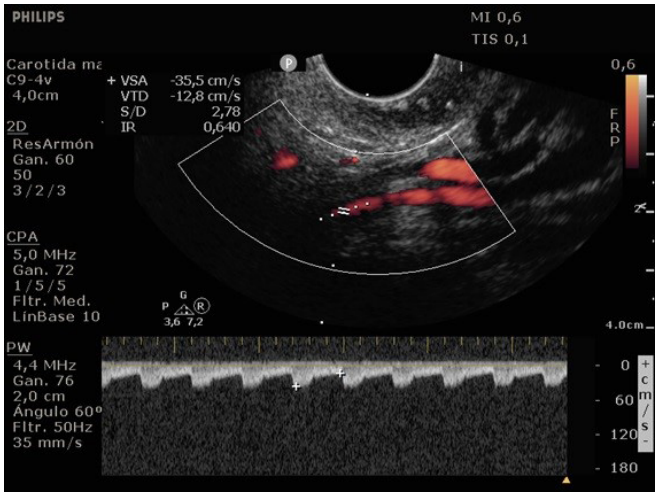


**Fig. 3.** Transoral ultrasonography using pulsed wave Doppler.

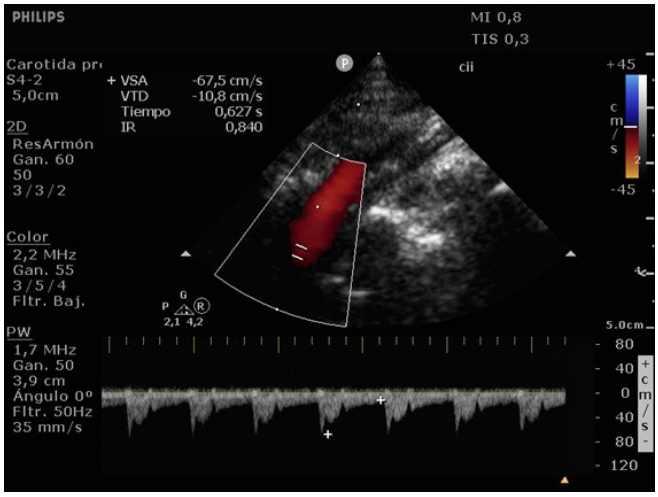


**Fig. 1.** Internal carotid artery conventional ultrasonography.

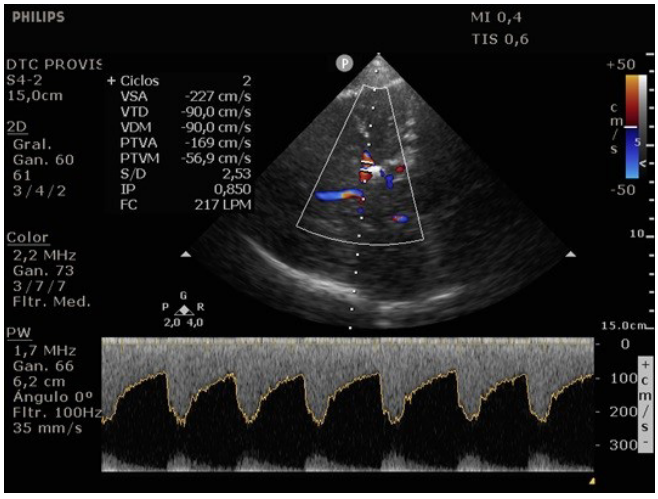


**Fig. 4.** Transcranial ultrasonography of the anterior cerebral artery.

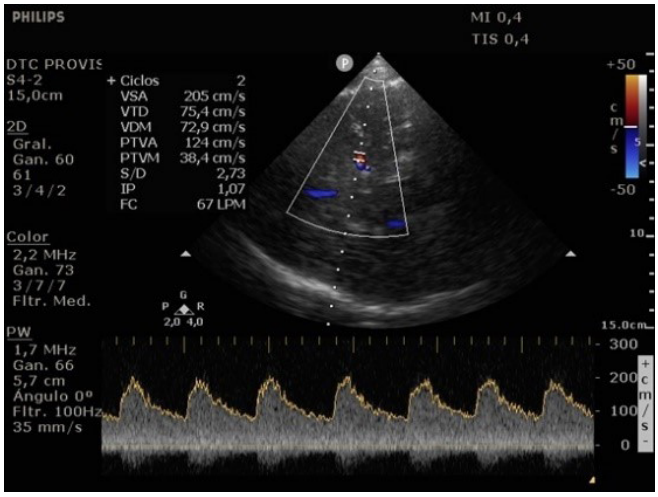


**Fig. 5.** Transcranial ultrasonography of the middle cerebral artery.

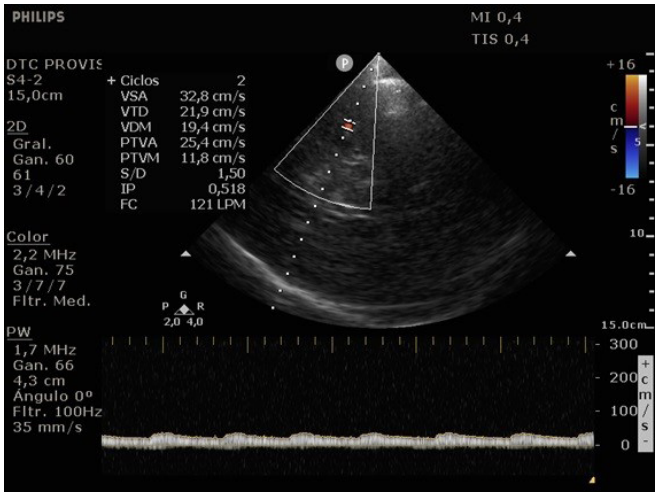


**Fig. 6.** Transcranial ultrasonography of the distal middle cerebral artery.

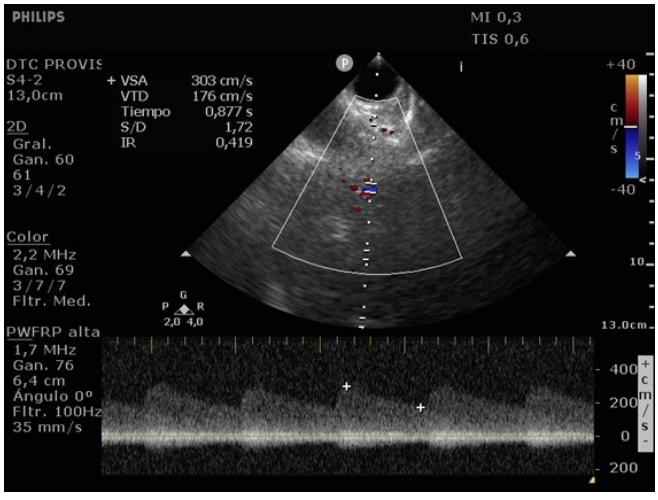


**Fig. 7.** Transorbital ultrasonography.

color Doppler mode, with the presence of very high velocities compatible with significant stenosis on the pulsed wave Doppler. Computed tomography angiography (CTA) of the neck and intracerebral vessels showed progressive lumen reduction at the distal portion of the left ICA until it became filiform and undetectable, along with the presence of flow in the intracranial arteries (Figs. 8 and 9). Brain magnetic resonance imaging detected positive diffusion-weighted imaging in the left MCA territory with hyperintensity at the left intracranial ICA in T2 compatible with the absence of emptied flow at the level of the petrous and cavernous portions of the artery (Fig. 10). The patient progressed with a

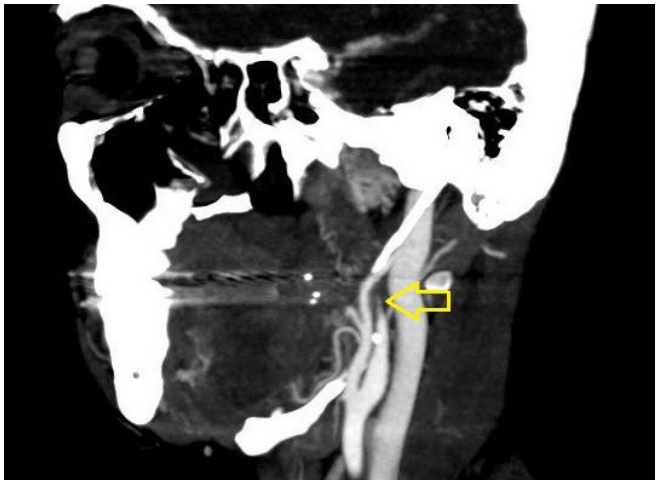

**Fig. 8.** Computed tomography angiography. Yellow arrow: postbulbar region of the left internal carotid artery (ICA) showing progressive reduction of the lumen until it becomes filiform and even undetectable compatible with ICA dissection.

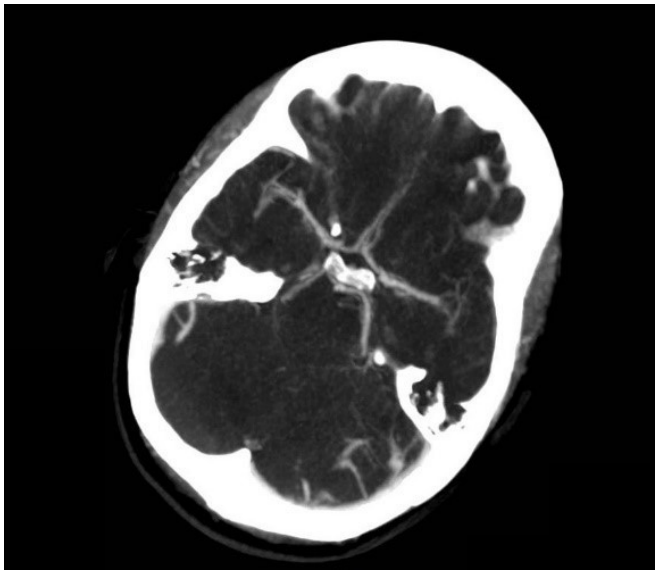

**Fig. 9.** Computed tomography angiography of the intracranial arteries.


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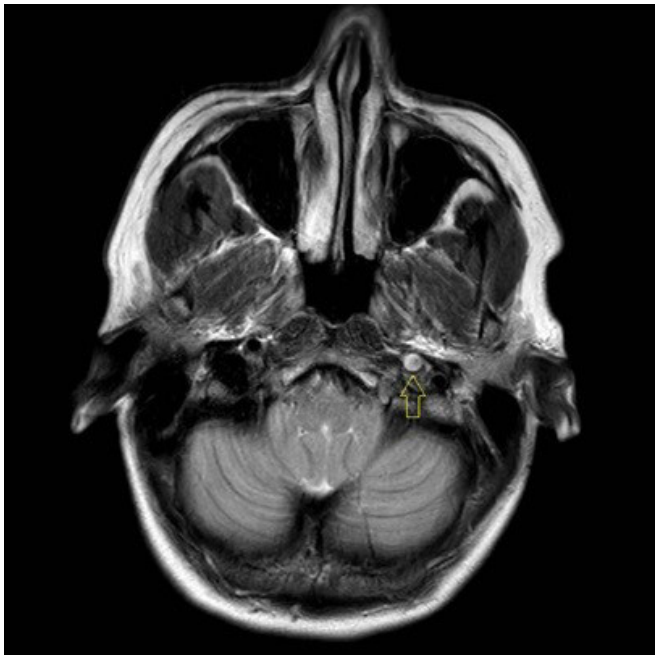

**Fig. 10.** Magnetic resonance imaging. Yellow arrow: absence of emptied flow at the level of the petrous and cavernous portion of the left internal carotid artery.

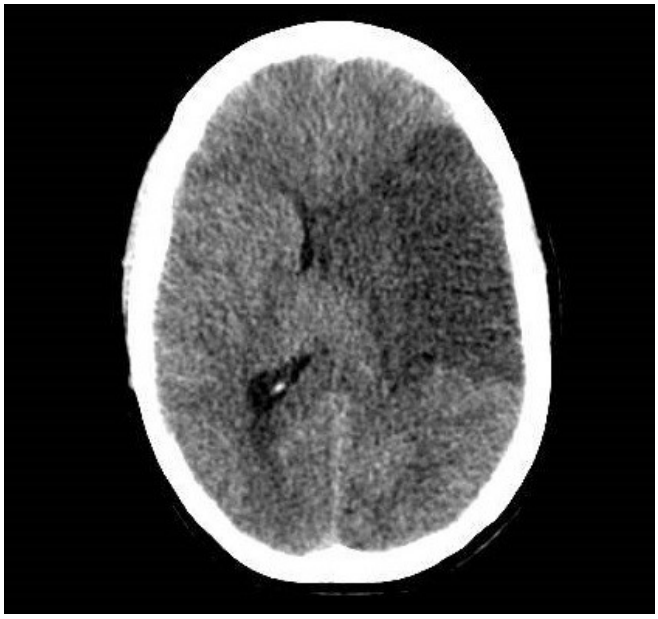

**Fig. 11.** Brain computed tomography of the patient in a coma.

Glasgow coma scale score of 8/15 and anisocoria with left mydriasis, requiring orotracheal intubation and mechanical ventilation support. We performed emergency head CT that showed extensive hypodensity in the left MCA territory with a 7-mm middle line shift (Fig. 11). We treated the patient with a hypertonic solution with partial reversal of mydriasis, and the neurosurgery team performed a left temporoparietal descompressive craniectomy. Despite surgical intervention, the patient developed mydriatic fixed pupils and lost the brain-steam reflexes. She was declared brain-dead in accordance with the criteria of the Argentinian death brain guidelines.

## DISCUSSION

ICA dissection occurs when the intima is damaged and dissects the ICA walls with the formation of a hematoma. It causes stenosis, occlusion, and thrombus embolization. The etiology can be traumatic or spontaneous and is frequently related to structural abnormalities, such as collagen disease. There are four primary diagnostic modalities: digital subtraction angiography, which is the gold standard, magnetic resonance angiography (MRA), CTA, and US. The latter is frequently performed during the initial assessment and serial imaging. However, conventional US cannot assess the distal portion of the ICA because the maxillary bone interferes [3-5]. The convex and sectorial probes can be used to overcome this difficulty, but the image quality in B mode when these probes are used is suboptimal. As the ICA ascends vertically behind the posterolateral pharyngeal wall, it is possible to evaluate it using a transoral approach with an endocavitary probe [3]. With this method, ICA dissection is visualized as a refinement in color Doppler mode, with low velocities in pulsed wave Doppler, as evidenced in our case [6].

Suzuki et al. [7] published a series of cases demonstrating the usefulness of transoral US in the diagnosis of ICA dissection, which is comparable to that of digital subtraction angiography and MRA. Benninger et al. [8] reported the usefulness of the combination of the assessment or neck and intracerebral vessels using US in the diagnosis of this entity, based mainly on identifying altered arterial flow patterns. Similar results were reported by Wang et al. [9] in the ultrasonographic assessment of patients with stroke.

In our case report, the transoral ultrasound approach identified ICA dissection. Transcranial Doppler showed increased velocities in the proximal portions of the MCA and ACA and intracranial portion of the ICA that were compatible with significant stenosis. This finding was interpreted as dissection of the distal ICA that extended to the intracranial portion, as suspected due to the results of brain MRA until its bifurcation in the MCA and ACA.

In the present case, we report the usefulness of ICA US using both conventional and transoral approaches with transcranial evaluation as a noninvasive method for the diagnosis of dissection of the distal extra and intracranial portion of the ICA, as well as

the involvement of the MCA in a patient with malignant cerebral infarction.

## ARTICLE INFORMATION

### Ethics statement

Approval for this study was waived in accordance with the local regulations because this study is a case report of a single patient and did not include protected health information, data analysis, or testing of a hypothesis, and was de-identified. Written consent was obtained from the patient before the publication of this case report.

### Conflict of interest

No potential conflict of interest relevant to this article.

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### Author contributions

Conceptualization: IC. Formal analysis: IC. Investigation: IC. Supervision: FMT. Writing–original draft: IC. Writing–review & editing: IC, VOC.

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# Morvan syndrome presenting with agrypnia excitata in post-thymectomy myasthenia gravis: a case report

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CASE REPORT

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**Background:** Morvan syndrome is characterized by neuromyotonia, dysautonomia, and various neuropsychiatric symptoms, as well as sleep disturbances, although these are less common than neuromuscular symptoms. Herein, we report a case of Morvan syndrome with peculiar sleep disturbances, documented via polysomnography.
**Case Report:** We present herein the case of a 67-year-old man who developed agitation and severe insomnia after undergoing a thymectomy for the treatment of myasthenia gravis, which was subsequently diagnosed as agrypnia excitata due to Morvan syndrome, based on 24-hour polysomnography.
**Conclusion:** We presented the 24-hour polysomnographic findings of a case of agrypnia excitata in Morvan syndrome. An extended polysomnography, however, might be helpful in analyzing sleep disturbances in Morvan syndrome.

**Keywords:** Morvan syndrome; Myasthenia gravis; Insomnia; Polysomnography; Thymoma

## INTRODUCTION

Morvan syndrome is an autoimmune disorder characterized by the following: (1) central nervous system dysfunction, such as neuropsychiatric symptoms, insomnia, and myoclonus; (2) autonomic symptoms, such as diffuse sweating and arrhythmia; and (3) peripheral hyperactivity, such as myokymia or neuromyotonia [1]. Agrypnia excitata, which is characterized by a loss of sleep along with motor and autonomic hyperactivity, is linked to three conditions: Morvan syndrome, fatal familial insomnia, and delirium tremens [2]. As Morvan syndrome is extremely rare, polysomnographic findings of agrypnia excitata in Morvan syndrome are not well established. Herein, we report the case of a patient with Morvan syndrome who underwent 24-hour polysomnography (PSG) after presenting with confusion, agrypnia excitata, cramping, hyperhidrosis, and myokymia. The patient had previously undergone a thymectomy for the treatment of myasthenia gravis (MG).

## CASE REPORT

A 67-year-old man presented with a 4-month history of general-

ized weakness, diffuse sweating, muscle twitching, and tingling pain. The patient had developed fatigable ptosis and neck weakness 2 years prior. Due to a diagnosis of MG with thymoma, which was positive for anti-acetylcholine receptor antibodies, a thymectomy was performed for the management of uncontrolled symptoms, despite adequate treatment. Improvement in the ptosis and generalized weakness continued for four months post-thymectomy; however, this was followed by muscle twitching through the whole limb, pain in the right leg, and limb weakness. Upon his admission to the hospital, agitation, nighttime confusion, hyperhidrosis, and persistent diffuse limb myokymia were observed. Electromyography revealed fasciculation potentials and myokymic discharges in the biceps and gastrocnemius muscles (Fig. 1), although magnetic resonance imaging of his brain was unremarkable. Paraneoplastic antibodies (anti-Hu, Yo, Ri, amphiphysin, CV2/CRMP5, Ma2/Ta [PNMA2], recoverin, Sox1, and Titin) were found to be normal, but anti-voltage-gated potassium channel (VGKC)-complex antibodies, particularly the anti-CASPR2 and anti-LGI1 antibodies, were unavailable.

The patient complained of symptoms of severe insomnia, such as difficulty falling asleep and maintaining sleep, as well as repeated short bouts of falling sleep and waking up throughout the day. Moreover, the patient displayed nocturnal agitation and complex sleep behaviors, for which rapid eye movement (REM) sleep behavior disorder was a differential diagnosis. As the patient's sleep-wake cycle seemed to be disrupted, the PSG study was performed over a 24-hour period, from 10:30 AM on the first day to 11:04 AM the next day (Fig. 2A). The patient slept for a total of 7 and 32 minutes over the 24-hour period. As sleep and wakefulness were irregularly distributed over the 24-hour period, a definite sleep-wake cycle could not be distinguished. The N1 and REM sleep durations were 405 minutes (89.6%) and 47 minutes (10.4%), respectively. Sleep spindles and K-complexes, which are N2 sleep and slow-wave sleep markers, respectively, were not observed. Complex movements of the hands and feet were consistently observed during both REM and non-REM sleep. Regarding REM-atonia dissociation, the absence of physiological REM-atonia was observed (tonic activity, 8.6%; phasic activity, 34.8%).

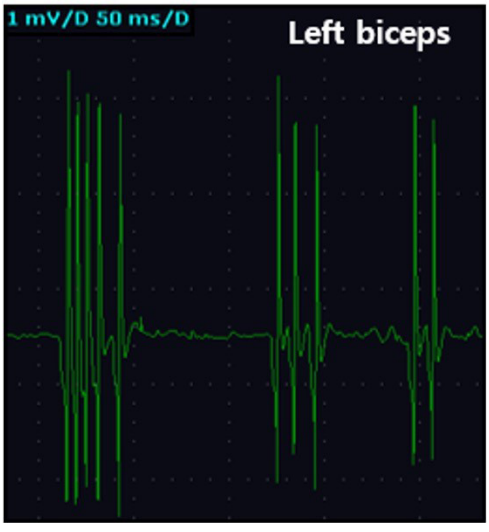


**Fig. 1.** Myokymic discharges in electromyography of the left biceps brachii muscle.

Heart rate variability analysis revealed sympathetic hyperactivity (low-frequency power/high-frequency power, 10.25) (Fig. 2B). No sleep apnea was identified, nor were any movements which could be classified as periodic limb movement disorders. The characteristics of the patient's PSG were consistent with those of agrypnia excitata (loss of sleep, confusion, and constant motor and autonomic hyperactivity). Treatment with gabapentin and carbamazepine improved neither the myokymia nor the tingling pain, and the patient was transferred to another hospital for palliative treatment.

## DISCUSSION

Morvan syndrome, an autoimmune disorder characterized by central, autonomic, and peripheral hyperactivity, is found to be highly associated with thymoma [1]. Although the impact of thymectomy on the occurrence of autoimmune disease is variable, thymectomy and thymoma chemotherapy may trigger a disease, which suggests that thymic tumors may also harbor antigenic targets. In particular, CASPR2 [3] and anti-VGKC antibodies are thought to play a pathogenic role in peripheral and central nervous system symptoms. Recent studies have shown that tests specific to CASPR2 and LGI1 antibodies are becoming more important in Morvan syndrome than those specific to VGKC-complex antibodies [1,4]. It is necessary to accurately diagnose and determine a course of treatment through antibody testing CASPR2 and LGI1 in patients with thymoma- or post-thymectomy-associated peripheral nerve hyperexcitability syndrome [1,5]. Unfortunately, in the present case, serologic testing for CASPR2 and LGI1 antibodies was not performed, and intravenous immunoglobulin therapy was not administered.

Agrypnia excitata is thought to be due to the functional blocking of the thalamo-limbic circuits that regulate the sleep-wake cycle and bodily homeostasis by VGKC antibodies [1,5]. As the diencephalic and brainstem nuclei are involved in both arousal and autonomic homeostasis, disruption of this homeostasis can result in both insomnia and autonomic dysfunction. The results of a previous study supported the evidence that VGKC subfamilies


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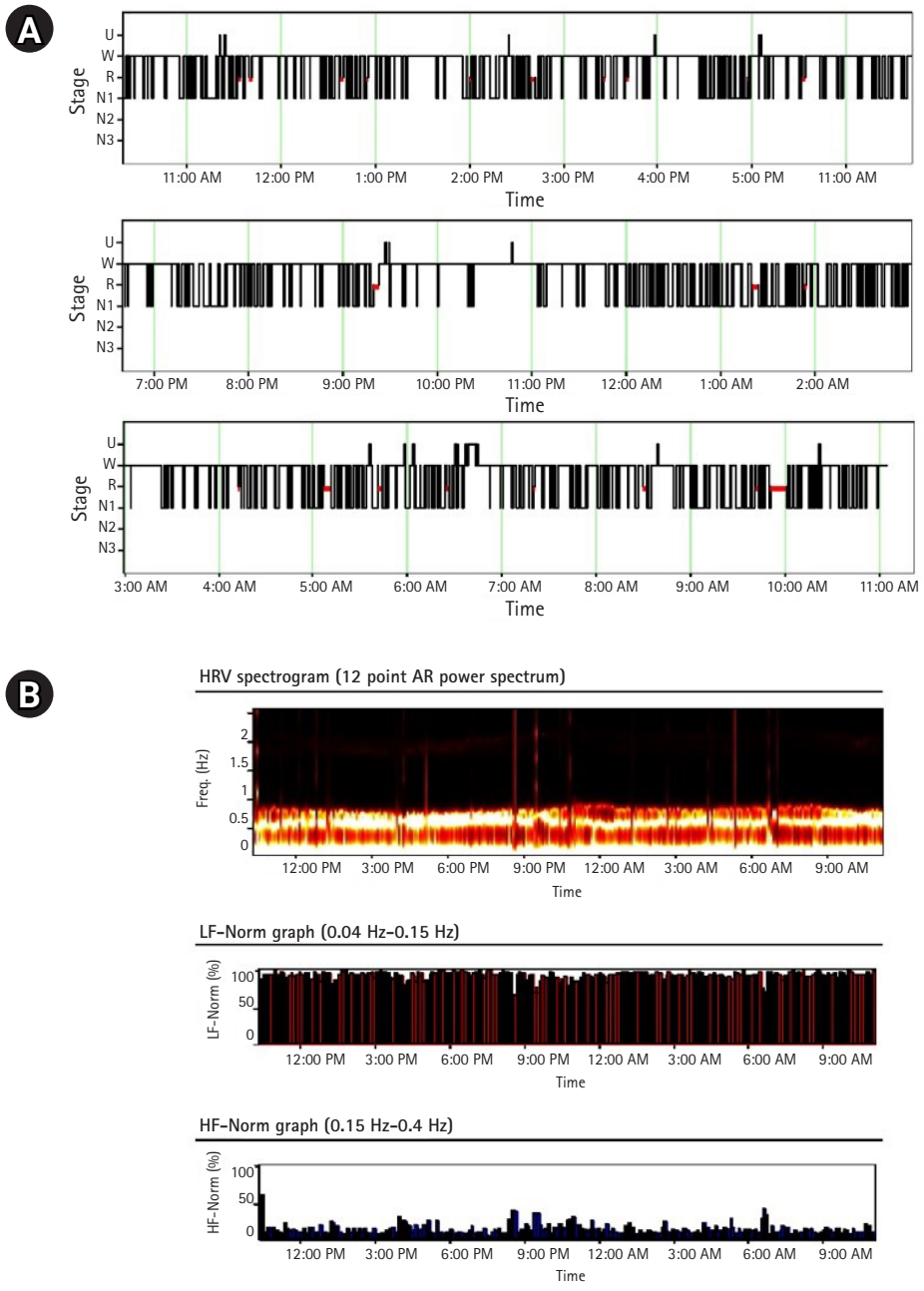


**Fig. 2.** (A) Hypnography over a 24-hour period and (B) heart rate variability (HRV) analysis. Widespread and small, fragmented block of sleep throughout a 24-hour period were identified. Note rapid eye movement sleep occupying most of the sleep period. U, undetermined sleep stage; W, wakefulness; R, rapid eye movement sleep; N, non-rapid eye movement sleep; AR, autoregressive; Freq, frequency; LF-Norm, normalized low frequency; HF-Norm, normalized high frequency.

are involved in sleep-wake cycle regulation [6], and indicated that mice lacking Kv-type potassium channels present with an increased motor drive and insomnia [7]. As in the case presented herein, agrypnia excitata is a key symptom differentiating Morvan syndrome from Isaac syndrome. Although a few studies largely support our findings, including recent polysomnographic studies in Korean men with fatal familial insomnia and a few studies with similar polysomnographic results [8-10], the results of present case suggest that widespread and small, fragmented blocks of sleep and wakefulness are not only mixed during the patient's sleeping hours, but also continue over a 24-hour period.

In summary, we have presented the case of a male Korean patient with agrypnia excitata due to Morvan syndrome, diagnosed after a thymectomy for the treatment of MG. The features of agrypnia excitata found through PSG were (1) the disruption of a normal sleep-wake cycle throughout a 24-hour period, (2) the

absence of sleep spindles and K-complexes, (3) the absence of slow-wave sleep, (4) complex actions during wakefulness and sleep, (5) increased muscle activity during REM and non-REM sleep, and (6) sympathetic hyperactivity. It is necessary to determine an accurate diagnosis and course of treatment by performing CASPR2 and LGI1 antibody tests in patients with thymoma- or post-thymectomy-associated peripheral nerve hyperexcitability syndrome and extended PSG testing.

## ARTICLE INFORMATION

### Ethics statement

The present study was approved by the Institutional Review Board (IRB) of Inje University Busan Paik Hospital, and the requirement for informed consent was waived due to the retrospective nature of the study. As such, the IRB approved an informed consent waiver.

### Conflict of interest

No potential conflict of interest relevant to this article.

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Conceptualization: SIO, KHJ. Data curation: all authors. Formal Analysis: all authors. Methodology: SIO, KHJ. Project administration: SIO, KHJ. Visualization: all authors. Writing–original draft: SIO, KHJ. Writing–review and editing: SIO, KHJ.

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# Urgent decompression of tension pneumomediastinum in a patient to relieve elevated intracranial pressure: a case report

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CASE REPORT

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**Background:** Timely recognition and intervention for venous outflow obstruction due to intrathoracic pathology are critical for controlling elevated intracranial pressure.
**Case Report:** A 26-year-old man with pectus excavatum and a posterior fossa tumor requiring biopsy, decompression, and cerebrospinal fluid diversion developed pneumomediastinum following intubation with tension physiology and progressive elevation of intracranial pressure. Emergent tracheostomy was performed to decompress intrathoracic pressure, augment venous return, and ultimately expedite the patient's definitive cancer therapy.
**Conclusion:** Recognition of the mediastinal pathology leading to venous obstruction may be required for the management of malignant intracranial hypertension. Tracheostomy may be a means to decompress mediastinal pressure and augment venous outflow in rare cases of pneumomediastinum with tension physiology.

**Keywords:** Mediastinal emphysema; Intracranial pressure; Case report

## INTRODUCTION

Patients in neuroscience intensive care unit (NSICU) frequently require invasive mechanical ventilation for concomitant respiratory failure. Intensivists need to pay special consideration to patients with elevated intracranial pressure (ICP) on invasive mechanical ventilation, particularly to ensure the maintenance of normal brain tissue oxygenation and optimal partial pressure of carbon dioxide ($PCO_2$) levels, and to provide sedation that achieves both comfort and optimal patient-ventilator synchrony. We report a case of a life-threatening complication of refractory ICP elevation and a well-recognized complication of invasive mechanical ventilation—pneumomediastinum. The pathophysiological mechanisms and proposed treatment strategies are discussed.

## CASE REPORT

A 26-year-old man with a distant history of chronic myelogenous

leukemia presented to the emergency department with headache, nausea, and vomiting. Computed tomography of the head revealed bilateral cerebellar lesions with surrounding vasogenic edema, resulting in a mass effect on the fourth ventricle and early tonsillar herniation. Subsequent biopsy was consistent with myeloid sarcoma, and the patient was started on steroids and whole-brain radiation. An external ventricular drain was placed due to progressive obstructive hydrocephalus on hospital day 7, but with progressive elevation of ICP, drowsiness, and poor tolerance of airway secretions, he was intubated and underwent suboccipital craniectomy on hospital day 12, with subsequent improvement of his ICP and associated symptoms. Postoperatively, the patient remained drowsy and struggled with impaired bulbar function and an inability to clear secretions, requiring continuous neurologic monitoring and prohibiting planned therapy with intrathecal chemotherapy and radiation. Although hemodynamically uncompromised, he ultimately needed reintubation due to respiratory fatigue on hospital day 14. Following an uncomplicated intubation, he was noted to have neck swelling and an increasing ICP trend. A computed tomography of the head and neck was ordered to rule out hematoma development in the setting of a recent suboccipital craniotomy (Fig. 1).

However, a post-intubation chest radiograph and subsequent examination revealed the presence of a new pneumomediastinum and subcutaneous emphysema (SQE) (Figs. 2 and 3). The patient continued to deteriorate clinically with rising ICP despite deep sedation. He had declining oxygen saturation despite a new 80% fraction of inspired oxygen ($FiO_2$) requirement and the application of 6 $cmH_2O$ of positive end-expiratory pressure. He also had been developing hypotension with intermittent electrical alternans that required the initiation of vasopressors. Tension physiology impairing the intracranial venous drainage was suspected. An emergent tracheostomy was performed to relieve the patient's tension pneumomediastinum while anticipating prolonged intubation, which might otherwise have limited his access to definitive therapy. Standard tracheostomy was performed midway between the sternal notch and thyroid cartilage at the level of the second tracheal ring, and allowed to heal by secondary intention to allow air to dissect across planes and relieve tension. A tracheostomy was successfully performed, resulting in decreased neck swelling, SQE, and pneumomediastinum. His ICP was noted to immediately decrease to 12–15 mmHg at the time of tracheostomy completion and remained stable for the following days; vasopressors were discontinued, and his oxygen requirements resolved. A limited proximal airway survey at the level of the segmental bronchi revealed no notable tracheal injury. The patient tolerated the transfer out of the NSICU for radiation therapy two days later. Ulti-

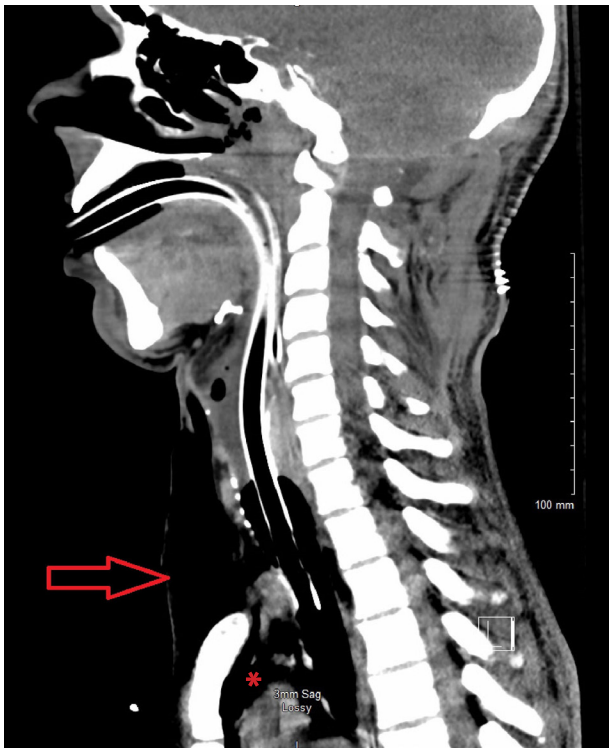


**Fig. 1.** Computed tomography scan of the neck. Sagittal section showing extensive supra-sternal subcutaneous emphysema (arrow) and retrosternal air (asterisk).

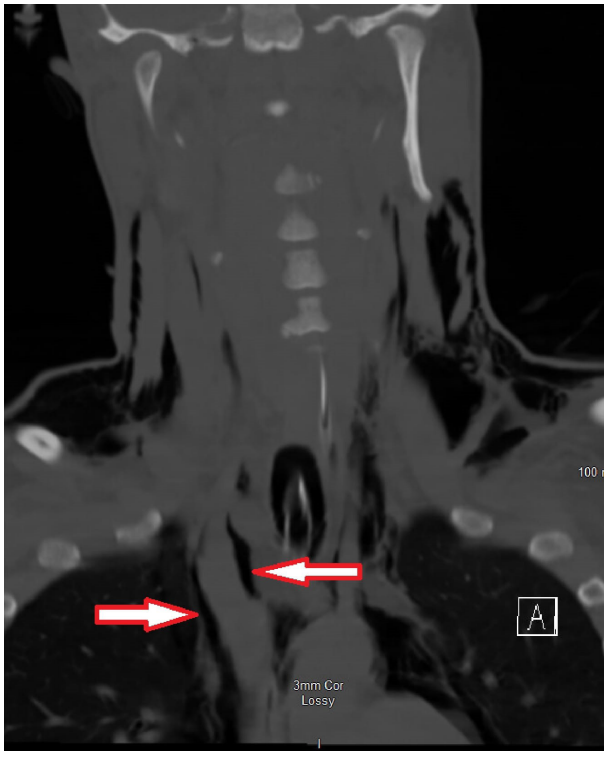


**Fig. 2.** Computed tomography scan of the neck. Coronal section showing air (arrows) around the right internal jugular and brachiocephalic veins.


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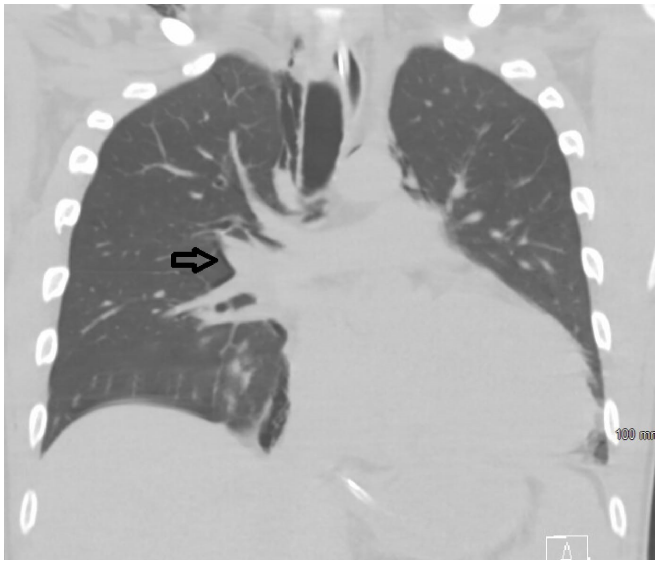

**Fig. 3.** Computed tomography scan of the chest. Coronal view showing air (arrow) around pulmonic vessels with the "Macklin effect."

mately, he required a ventriculoperitoneal shunt and was decannulated prior to being discharged home after a 103-day length of stay.

## DISCUSSION

Successful management of intracranial hypertension is crucial to mitigate morbidity and mortality in neurocritical care. The tiered approach recommended for treatment starts with tier 0, which includes the management of pain, fever, anxiety, and proper positioning of the patient. Neutral positioning of the neck and elevation of the head of the bed to 30°; the proposed mechanism is the maximization of cerebral venous outflow and subsequent lowering of ICP [1]. Our case demonstrates how proper assessment of the cardiovascular and respiratory systems and early recognition of this rare complication can lead to improvements in our approach to lower ICP.

Intracranial pathology leading to acute respiratory failure may, in turn, intensify detrimental effects on the acutely injured brain. Respiratory failure, whether secondary acute hypoxic, hypercapnic, or ineffective ventilation due to inability to protect the airway from secretions or upper airway obstruction, is common in the NSICU [2]. The cilia of the nasopharynx function to propel secretions in a caudal direction, whereas those of the lower airways propel secretions in a cephalad direction. These secretions then accumulate in the pharynx to be swallowed or expectorated through complex airway protective mechanisms, which may be significantly impaired in neurological injury [3,4]. In the present case, posterior fossa pathology and direct brainstem compression leading to bulbar pathology presented a risk of acute aspiration and respiratory insufficiency. Increased work of breathing in patients with limited arousal and variable strength requires vigilance that may prohibit disposition from the intensive care unit or, as in this case, lead to intubation for airway protection.

Pneumomediastinum is a rare complication of intubation, although it was likely a higher risk in our patient due to the baseline anatomic abnormality of the pectus excavatum. Air accumulation, worsened by the application of positive pressure ventilation, led to rapid accumulation of mediastinal and subcutaneous air. Pneumomediastinum, with or without SQE, is a well-recognized complication of invasive mechanical ventilation. Alveoli may rupture due to different mechanisms, including alveolar hyperinflation and/or dynamic airway obstruction with increased intra-alveolar pressure. Air then escapes the alveolar space into the interstitium, dissecting its way from the peri-alveolar space following the bronchovascular structures to the hilum, and then accumulates in the mediastinum and up to the soft tissue of the neck, resulting in pneumomediastinum and concomitant SQE. This ascending pathway was described by Macklin [5] in 1939.

Pneumomediastinum is usually benign and well-tolerated by most patients. However, tension physiology has been described experimentally in the works of Macklin [5] through compression of the pulmonary veins, leading to increased afterload of the right ventricle. While pneumomediastinum does not typically cause rapid pressurization of the intrathoracic space, chest wall and parenchymal compliance may be restricted by the underlying anatomic or pathologic conditions. Patients may develop pneumopericardium and tension physiology that resembles tamponade [6,7]. If sufficient to cause hemodynamic compromise and shock, particularly obstructive physiology with evidence of electrical or pulsus alternans, narrowing of pulse pressures, and worsening hypoxia and/or hypotension, it follows that venous return from the intracerebral vasculature to the right heart will be limited [8]. In our case, the patient had progressive tension pneumomediastinum, likely in the setting of chronic restrictive lung disease; this clinically resulted in the direct compression of intrathoracic structures as well as vasculature in the neck, leading to a rapid rise in intracranial pressure and clinical deterioration.

Treatment of pneumomediastinum is usually achieved conservatively if not associated with hemodynamic compromise or other end-organ perfusion compromise (i.e., tension pneumomediastinum), and it may take one to two weeks for air to be fully absorbed in the absence of additional inspiratory pressures. On the other hand, tension pneumomediastinum can be fatal if not recognized and treated promptly. Similar to treating tension pneu-

mothorax, rapid decompression of air to equilibrate the pressure gradient is desired. Surgical decompression (i.e., mediastinotomy) proposed by Macklin can be achieved through chest tube insertion in the subxiphoid region or through a simple suprasternal incision [5,8]. A simple incision might be more appealing in cases with no continuous air leak or in emergent conditions in which there is clear communication between the mediastinal air and suprasternal subcutaneous tissue.

Our patient developed refractory ICP elevation, hemodynamic compromise, and evidence of rapidly progressive obstructive shock, all of which resolved immediately after performing tracheostomy. Although higher than suprasternal mediastinotomy, pressurized air dissection through tissue planes along the path of least resistance to a tracheotomy site was sufficient to depressurize the neck and thorax, alleviating direct compression of the jugular veins and mediastinal structures, allowing right ventricular filling, and consequently, promoting cerebral venous drainage. We postulate that there is a critical pressure point beyond which further accumulation of air in the mediastinum leads to impaired venous drainage in the brain. In patients with refractory ICP elevation, we propose to routinely assess for the presence of SQE and pneumomediastinum. To our knowledge this is the first case of an adult with refractory ICP elevation due to pneumomediastinum. Furthermore, decompression of the pneumomediastinum is not often necessary, and tracheostomy may be considered in the rare event when intervention is required.

## ARTICLE INFORMATION

### Ethics statement

The Institutional Review Board approved this study protocol with a waiver of informed consent as the patient was deceased at the time of data curation.

### Conflict of interest

No potential conflict of interest relevant to this article.

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# Malignant cerebral infarction after COVID-19 myocarditis in 22-year-old female: a case report

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CASE REPORT

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**Background:** Ischemic stroke is one of the serious neurological complications of coronavirus disease 2019 (COVID-19). However, ischemic stroke can develop secondary complications after cardiac involvement in COVID-19.
**Case Report:** We report the case of a 22-year-old patient who presented with malignant cerebral infarction 10 months after COVID-19-related myocarditis. A 22-year-old woman was referred to the emergency room because of abnormal mental status changes. She developed heart failure and arrhythmia after COVID-19-related myocarditis. Brain magnetic resonance imaging (MRI) revealed high signal intensity on diffusion-weighted imaging that was indicative of acute cerebral infarction in the left middle cerebral artery (MCA) and left anterior cerebral artery (ACA) territory. In addition, occlusion of both the left MCA and ACA was observed on brain MRI. Craniectomy with therapeutic hypothermia was performed to treat the cerebral edema.
**Conclusion:** This case suggests that caution is needed in survivors with secondary complications after COVID-19.

**Keywords:** COVID-19; Myocarditis; Ischemic stroke; Case report

## INTRODUCTION

Since the first case of pneumonia caused by coronavirus disease 2019 (COVID-19) was detected in Wuhan City in China in December 2019, COVID-19 has been the most prevalent infectious disease in the modern medicine era [1]. Although COVID-19 mainly causes respiratory infection, another wide spectrum of clinical diseases, including cardiovascular and neurological complications that the virus itself causes, have been elucidated [2,3]. In particular, ischemic stroke is one of the neurological complications of COVID-19. It could be caused by coagulation abnormalities or vascular endothelial injury caused by the virus [4]. However, cardioembolic stroke, which accounts for approximately 20% of the total causes of ischemic stroke, could develop secondary manifestations of cardiac involvement of the virus [5]. Herein, we report the case of a 22-year-old patient who presented with malignant cerebral infarction 10 months after COVID-19-related myocarditis.

## CASE REPORT

A 22-year-old woman was referred to our institution's emergency room because of a sudden change in mental status. She had a history of COVID-19, which she had contracted during a COVID-19 outbreak in Daegu, South Korea, 10 months earlier. On the patient's initial admission for COVID-19, the main complaint was acute chest pain with dyspnea. On physical examination, her blood pressure was 100/60 mmHg, and body temperature was 38°C. Considering that the entire world is amid the COVID-19 pandemic, a polymerase chain reaction test for COVID-19 using a nasopharyngeal swab was performed, and the result came back positive. Laboratory examination revealed a lymphocyte-dominant white blood cell count of 1,212 uL. The C-reactive protein level was 0.6 mg/dL. In addition, brain natriuretic peptide and troponin I levels were 1,929 pg/mL (reference range, < 125 pg/mL) and 1.26 ng/mL (reference range, < 0.3 ng/mL), respectively. Chest radiography revealed diffuse multifocal consolidation in both lung fields with cardiomegaly. Electrocardiography (EKG) revealed an intraventricular conduction delay and premature complexes. Echocardiography revealed severe left ventricular dysfunction.

Multimodal imaging was performed to diagnose COVID-19-related myocarditis. A biopsy is a helpful and precise method for diagnosing myocarditis [6]; however, it cannot be performed because of the risk of COVID-19 infection. Cardiac computed tomography (CT) showed multifocal consolidation with ground-glass opacities in the lungs (Fig. 1A) and hypertrophied myocardium due to edema (Fig. 1B). Cardiac magnetic resonance imaging (MRI) showed transmural late gadolinium enhancement (Fig. 1C), indicative of myocarditis. Treatment was initiated with lopinavir/ritonavir for seven days with diuretics. At the time of discharge, the ejection fraction was 28%, with severely decreased global wall motion in the left ventricle (LV) and a dilated left atrium (LA) noted on transthoracic echocardiography (TTE; LA volume index, 58.3; LV volume index, 107.78). Nonsustained ventricular tachycardia was also observed. Subsequently, she was followed up in the outpatient department and treated with sacubitril/valsartan and diuretics. During follow-up, EKGs were performed frequently, no atrial fibrillation (AF) was detected, no intracardiac thrombus was observed, and no significant change in the LA and LV volume index on TTE was noted.

On her second most recent admission for cerebral infarction, the patient saw her parents off to work at 8:00 AM. Her parents

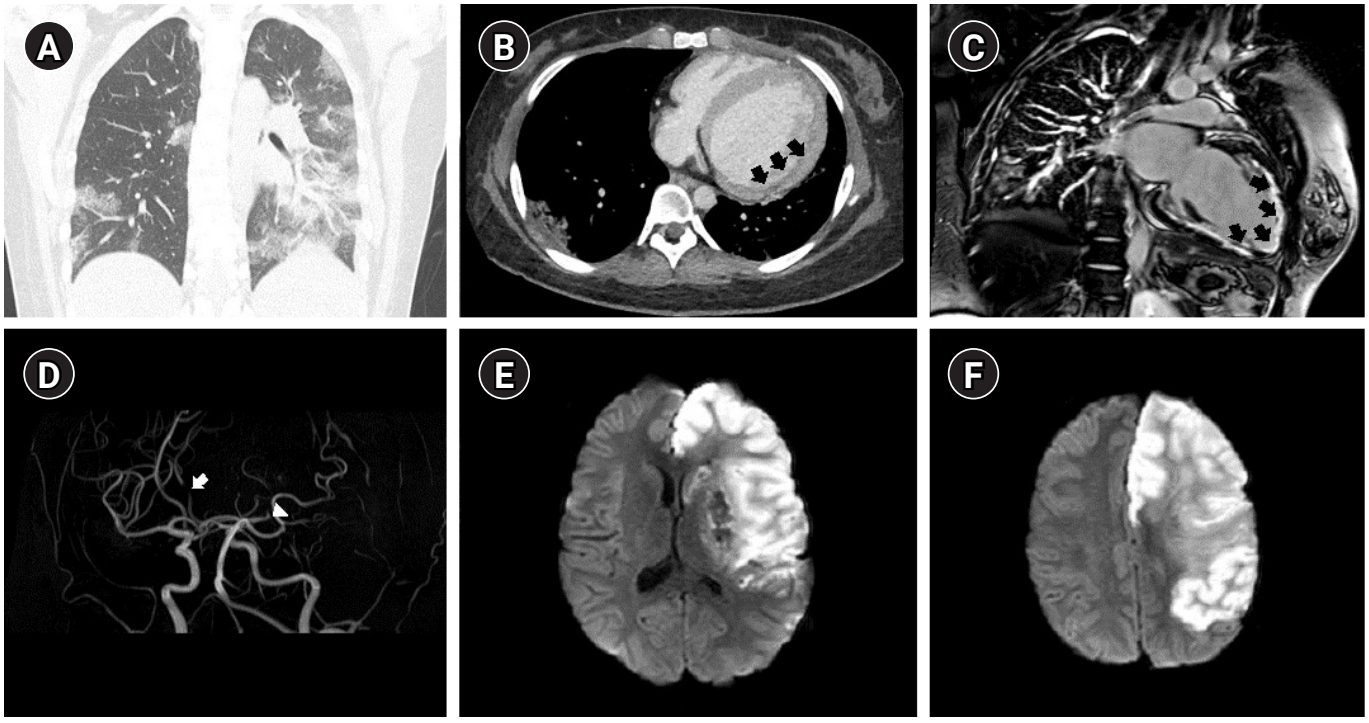


**Fig. 1.** (A) Chest computed tomography showing multifocal consolidation with ground-glass opacities in both lungs. (B) Cardiac magnetic resonance imaging showing a hypertrophied myocardium due to edema (black arrows). (C) Cardiac magnetic resonance imaging showing transmural late gadolinium enhancement (black arrows). (D) Brain magnetic resonance angiography showing the severe stenosis of the left A2 segment of the anterior cerebral artery (ACA; white arrow) and the distal segment of the left middle cerebral artery (MCA; white arrowhead). (E, F) A diffusion-weighted image showing high signal intensity in the left MCA and ACA territory infarction.


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discovered her 10 hours later with an altered mental status. On neurological examination, the patient was drowsy with notable global aphasia. According to the Medical Research Council grading system, the power of the right upper extremity was 1/5, whereas that of the right lower extremity was 2/5. The total National Institute of Health Stroke Scale score was 18 (level of consciousness [LOC] question, 2; LOC command, 2; best gaze, 2; facial palsy, 2; right arm motor, 2; right leg motor, 2; sensory, 1; best language, 3; dysarthria, 2). EKG revealed AF that was not previously detected during the follow-up examinations in the outpatient department. Diffusion-weighted brain MR revealed high signal intensity in the left middle cerebral artery (MCA) and left anterior cerebral artery (ACA) (Fig. 1D). MR angiography demonstrated severe stenosis of the left ACA and occlusion of the left MCA (Fig. 1E). One day after admission, a follow-up brain CT scan indicated that a subfalcine herniation had developed (Fig. 1F), and craniectomy was immediately performed.

To manage brain edema after craniectomy, intravenous D-mannitol was administered, and therapeutic hypothermia was applied using a surface cooling device (Arctic Sun) at a target temperature of 34°C. Light sedation with dexmedetomidine was administered during hypothermic induction, and the target mean arterial pressure was set at >60 mmHg to maintain cerebral perfusion pressure. Acetaminophen and buspirone were administered to control the shivering. If the two drugs were unable to control the shivering, additional intravenous pethidine was administered. The heart rhythm was controlled using intravenous amiodarone (class III, anti-arrhythmic drug), and furosemide was administered to prevent fluid retention. Gradually, her mental status improved from drowsiness to alertness when she was moved from the intensive care unit to the general ward. On TTE, the LA volume index increased to 80.41 Compared with previous findings (previous LA volume index, 58.3). The patient was discharged on apixaban for anticoagulation, sacubitril/valsartan, diuretics, and amiodarone one month after admission. Three months after discharge, the patient was able to stand with assistance, and her global aphasia improved to transcortical motor aphasia. Despite neurological improvements, there was no improvement in cardiac function based on TTE findings compared to the findings at discharge.

## DISCUSSION

COVID-19 can directly invade the myocardium and cause myocarditis [7]. This may be due to the affinity of the virus for angiotensin-converting enzyme 2 (ACE2), which acts as a portal for viral entry and ACE2 downregulation, leading to myocardial dysfunction [8]. Therefore, myocarditis should be suspected in patients with COVID-19 with acute chest pain and elevated cardiac enzyme levels. In addition, myocarditis is associated with secondary complications such as malignant tachycardia and heart failure [9]. In our case, the patient exhibited acute chest pain and elevated cardiac enzyme levels after COVID-19 infection; myocarditis was confirmed by cardiac CT and MRI [10]. At discharge, the patient had severely decreased LV wall motion, and a dilated LA was noted on TTE with recurrent ventricular tachycardia. Additionally, AF was noted in the patients in the emergency room. All of these conditions are high-risk cardioembolic causes of ischemic stroke. Therefore, fulminant complications of COVID-19-related myocarditis could have contributed to the development of ischemic stroke in our patient.

In this case, AF was not documented during frequent EKG monitoring in the outpatient department. However, the patient also had several high-risk cardioembolic sources. Therefore, preventive anticoagulation therapy should be considered in such cases. In this regard, there have been several reports on the benefits of preventive anticoagulation for heart failure [11]. In addition, to find the cover AF, frequent 24-hour Holter monitoring or an implantable loop recorder should be considered.

The cumulative number of confirmed COVID-19 cases worldwide has surpassed four billion. This means that the number of survivors with secondary complications after COVID-19 is expected to increase proportionally. Therefore, preventing disease transmission is imperative; however, focusing on survivors with secondary complications after COVID-19 may also be crucial because the long-term sequelae of COVID-19 may lead to serious conditions such as ischemic stroke.

Further analysis is vital to clarify the extent of COVID-19-related cardiovascular complications and prevent the occurrence of ischemic stroke. In addition, prophylactic anticoagulation should be considered in patients at a high risk of venous and arterial thromboembolism after COVID-19 infection.

## ARTICLE INFORMATION

### Ethics statement

This study was reviewed and approved by the Institutional Review Board of Keimyung University Dongsan Hospital (IRB No. 2002-03-007). The requirement for informed consent was waived.

### Conflict of interest

Jeong-Ho Hong is an editorial board member of the journal but he was not involved in the peer reviewer selection, evaluation, or

decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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# Recanalization of the middle cerebral artery after prolonged induced hypertensive therapy to rescue early neurologic deterioration: a case report

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CASE REPORT

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**Background:** Although decades have passed since the introduction of pharmacologically induced hypertensive therapy (PIHT) against early neurologic deterioration (END) in acute ischemic stroke, the optimal duration of PIHT remains elusive.
**Case Report:** A 70-year-old man developed right hemiplegia and aphasia 25 hours before arrival. Computed tomography angiography (CTA) revealed acute infarction in the left middle cerebral artery (MCA) territory and occlusion of the left internal carotid artery. He experienced END 36 hours after admission, and CTA revealed a newly developed proximal MCA occlusion. PIHT was initiated to augment cerebral perfusion. As his neurologic symptoms were highly dependent on blood pressure, PIHT was inevitably sustained for over 3 weeks. Follow-up CTA revealed recanalization of the MCA.
**Conclusion:** Although further investigation is required to expedite the future clinical application, prolonged PIHT may serve as a viable collateral-enhancing treatment for a certain subset of patients with END without alternative treatment options.

**Keywords:** Ischemic stroke; Clinical deterioration; Phenylephrine; Middle cerebral artery; Case report

## INTRODUCTION

Early neurologic deterioration (END) is a common complication occurring in up to one-third of patients with acute ischemic stroke [1]. Proximal arterial occlusion is a risk factor for predicting END [2]. Pharmacologically induced hypertensive therapy (PIHT) is a therapeutic option for END, which acts by increasing collateral flow, thereby preventing the expansion of the infarct core [3,4]. Phenylephrine is mainly used for PIHT because it selectively binds to alpha-1 receptors and causes peripheral vasoconstriction without substantial direct cerebral vasoconstriction to increase blood pressure (BP) [5]. However, PIHT is not always safe, as it may lead to adverse effects such as hemorrhagic transformation, cerebral edema, and ischemic heart diseases [4]. For this reason, PIHT is generally performed within 3–5 days [4,6]; however, such recommendations are merely based on theoretical arguments and case reports. Herein, we report a patient with acute internal carotid artery (ICA) terminus occlusion who was successfully treated with prolonged PIHT over 3 weeks, which far exceeds the conventional safe window for PIHT.

## CASE REPORT

A 70-year-old man with a history of hypertension and dyslipidemia presented with aphasia and weakness of the right arm (11 hours from the last known normal) was referred to our hospital 14 hours after the detection of symptoms by a regional hospital. Upon neurological examination, he showed motor aphasia, dysarthria, and right arm weakness (initial National Institutes of Health Stroke Scale [NIHSS] score, 7). Brain computed tomography (CT) revealed a hypodense lesion in the superior division of the left middle cerebral artery (MCA) territory, and CT angiography (CTA) revealed occlusion of the left ICA with well-developed collateral circulation from the anterior communicating artery (Fig. 1A and B). Although perfusion mismatch was observed on perfusion CT processed by the RAPID software (iSchemaView, Menlo Park, CA, USA) (cerebral blood flow [CBF] < 30%, volume: 23 mL; Tmax > 6.0 seconds, volume: 101 mL) (Fig. 1C), endovascular therapy (EVT) was not performed as 25 hours had passed since the last known normal beyond the extended time frame for EVT. Brain magnetic resonance imaging (MRI) demonstrated acute lesions in the MCA superior division territory on diffusion-weighted images (DWI) with hyperintensity on fluid-attenuated inversion recovery (FLAIR) images (Fig. 1D and E). He was prescribed dual antiplatelet (aspirin and clopidogrel) and high-dose statin therapy, and his neurological symptoms improved thereafter (NIHSS score, 5).

However, the patient developed abrupt neurologic deterioration 33 hours after admission (BP, 117/60 mmHg) with dense right hemiplegia (motor grade 2) and global aphasia (NIHSS score, 17). Follow-up CTA revealed a newly developed left proximal MCA occlusion (Fig. 2A). Despite the definite perfusion mismatch (CBF < 30%, volume: 26 mL; Tmax > 6.0 seconds, volume: 175 mL) (Fig. 2C), EVT was not considered because of concerns about the possibility that the device could not access the target vessel due to left proximal ICA occlusion and the risk of hemorrhagic transformation after recanalization. Instead, triplet antiplatelet therapy (aspirin, clopidogrel, and cilostazol) and PIHT were initiated to raise the systolic BP above 140 mmHg, and he showed significant improvement (NIHSS score, 11) 10 hours after administering phenylephrine (BP, 145/78 mmHg). Initially, phenylephrine (0.1 mg/mL) was intravenously infused at a rate of 10 mL/hr (1 mg/hr, 0.28 μg/kg/min) and the dose was increased up to a rate of 35 mL/hr (3.5 mg/hr, 0.97 μg/kg/min). Brain MRI demonstrated a newly developed acute lesion in the basal ganglia and corona radiata (Fig. 2D). As the symptoms plateaued for 10 days after PIHT, the dose of phenylephrine was gradually tapered. However, phenylephrine was not discontinued because his neurologic symptoms were highly dependent on BP and showed abrupt deterioration (aphasia and hemiplegia) when phenylephrine was tapered even at a minimal rate (5 mL/hr). Thereafter, phenylephrine was administered at 35 mL/hr (3.5 mg/hr, 0.97 μg/kg/min) for 4 more days, following which the infusion rate was lowered by 5 mL/hr per day for 7 days, and phenylephrine was discontinued 21 days after the start of PIHT. The patient did not show neurologic deterioration upon dose reduction, and the therapy was discontinued 24 days after the onset of END. No abnormalities in cardiac enzymes, electrocardiogram, or chest radiography were noted during this period. Unexpectedly, follow-up perfusion CTA revealed recanalization of the MCA occlusion and improved perfusion status (Tmax > 6.0 seconds, volume: 0 mL) (Fig. 3A-C). There were no further ischemic lesions on follow-up DWI or FLAIR images (Fig. 3D and E). The patient was discharged 31 days after symptom onset, with significantly improved neurological symptoms (NIHSS score, 6). He did not experience any recurrent stroke symptoms until 18 months after discharge.

## DISCUSSION

Although the definition of END varies, most studies have been based on a worsening NIHSS score of 4 or more within 24–72 hours after the onset of acute ischemic stroke [2]. Symptomatic intracranial hemorrhage and malignant vasogenic edema are known to be the main causes of END; however, the exact mechanism of END is unknown in approximately half of the cases. If a clear mechanism cannot be identified, it is possible that the patient's prognosis may deteriorate because appropriate treatment cannot be provided. It is hypothesized that the extension of symptomatic ischemic tissue is the mechanism by which END occurs without a clear reason [7]. In a study of minor stroke patients with proximal occlusion, it was determined that END may occur [8] because there is a high risk of ischemic penumbra enlargement in the presence of a proximal occlusion, followed by an increase in infarction volume. Since our patient had an NIHSS score of 7 with ICA occlusion, it would have been an indication for EVT if the patient had visited within the EVT time frame. However, our patient was transferred from another hospital, thereby going beyond the time frame for EVT. The best medical management was started because EVT was not performed; however, the patient's neurological deficit was presumed to have worsened due to proximal occlusion. PIHT was performed as a treatment for END.

Managing patients with END is challenging in daily clinical practice. The clinical situation is complicated; therefore, a substantial proportion of patients are not subjected to treatment sup-


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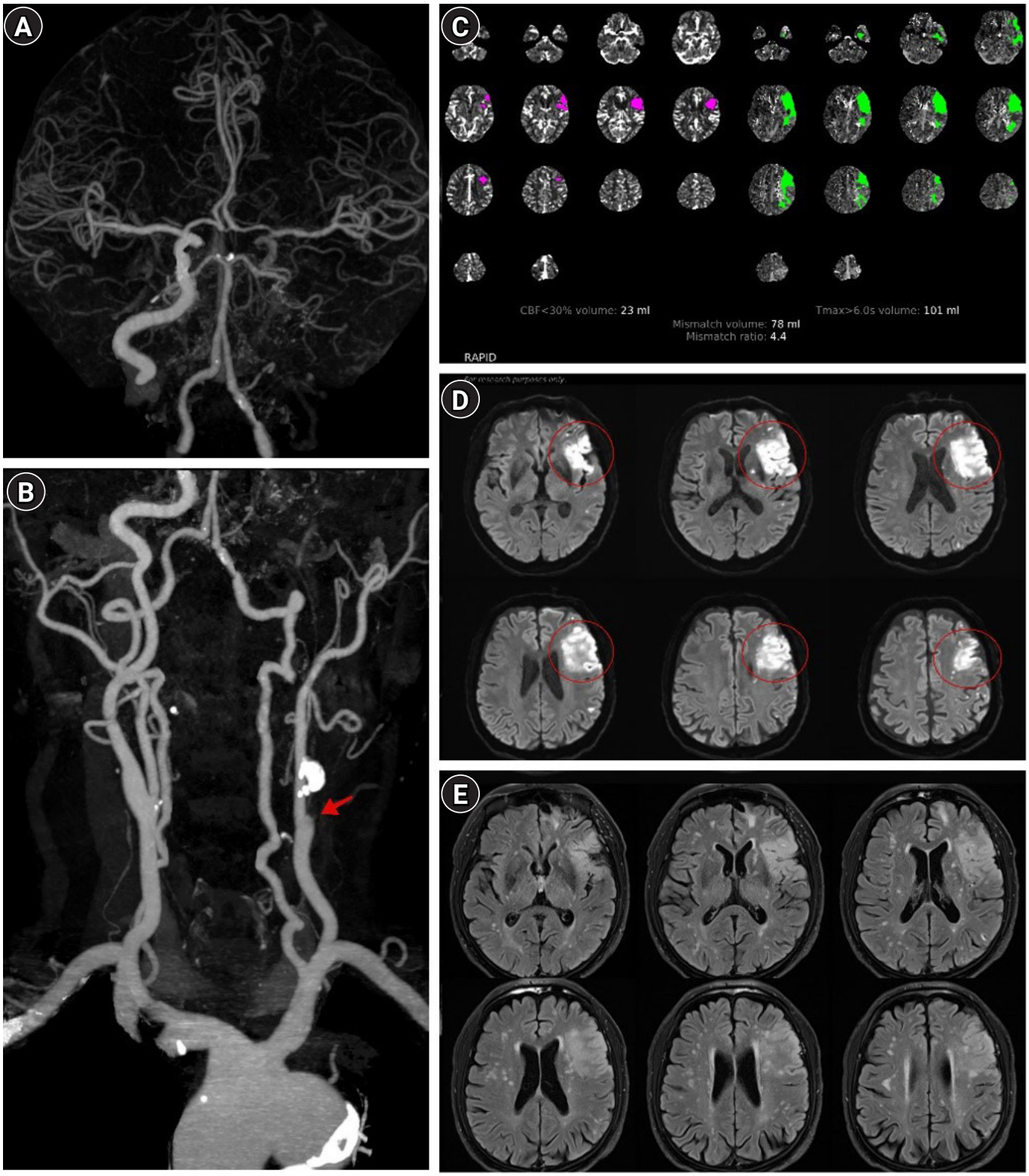


**Fig. 1.** Brain perfusion computed tomography angiography (CTA) and magnetic resonance imaging (MRI) at admission. (A) Brain CTA revealed collateral flow via the anterior communicating artery to the middle cerebral artery (MCA) and (B) left proximal internal carotid artery occlusion with calcification (arrow, spearhead shape). (C) Perfusion mismatch was confirmed by the RAPID software (iSchemaView, Menlo Park, CA, USA) (cerebral blood flow [CBF] <30%, volume: 23 mL; Tmax >6.0 seconds, volume: 101 mL). (D) Brain MRI revealed increased signals on the diffusion-weighted imaging sequence in the left MCA superior division territory (red circles) and (E) on the fluid-attenuated inversion recovery sequence at the same lesion.

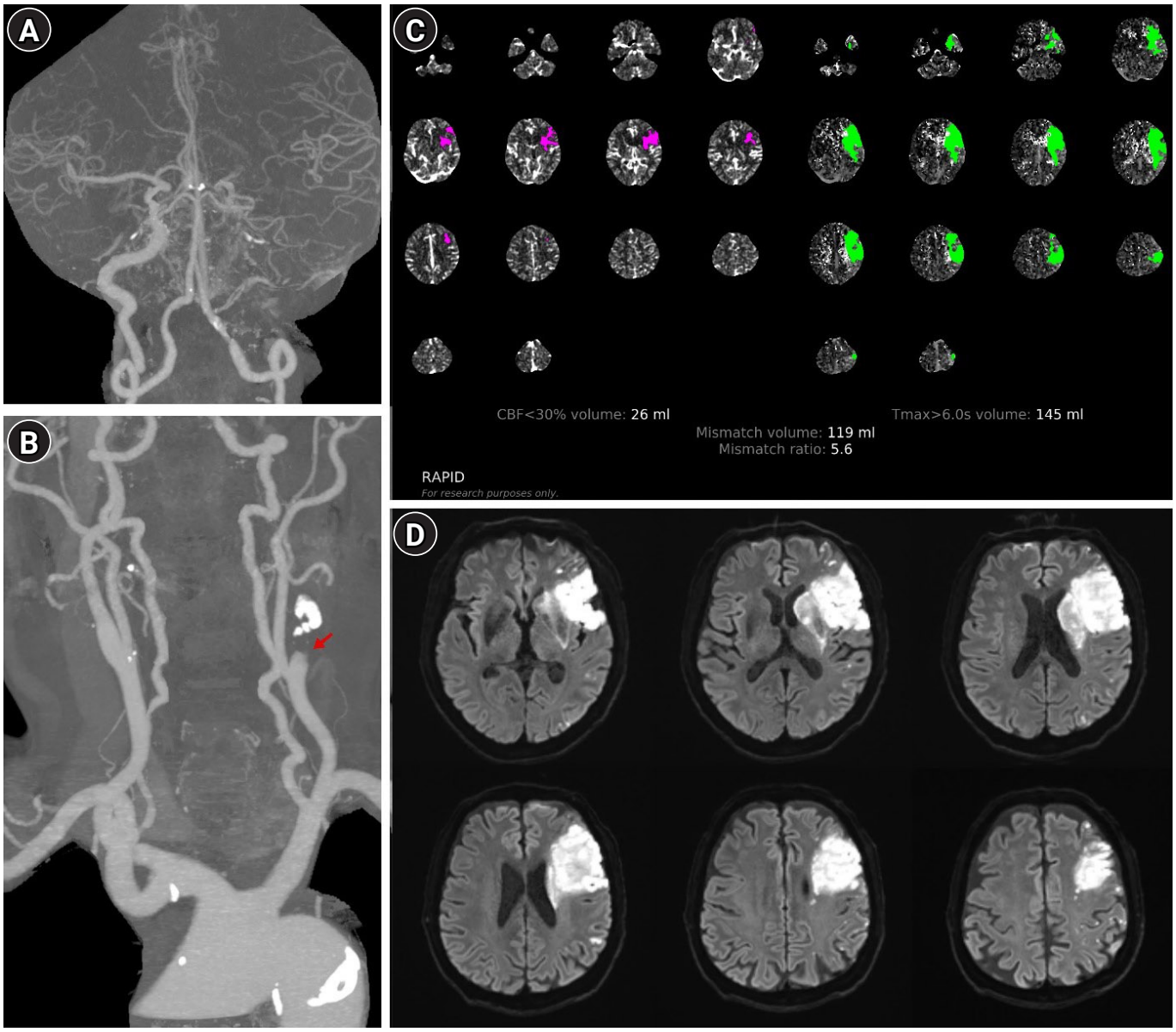


**Fig. 2.** Brain perfusion computed tomography angiography (CTA) and magnetic resonance imaging after early neurologic deterioration. (A) Brain CTA revealed left proximal middle cerebral artery occlusion and (B) changes in the shape of the internal carotid artery occlusion (arrow, stump shape). (C) Perfusion mismatch identified using the RAPID software (iSchemaView, Menlo Park, CA, USA) was further expanded (cerebral blood flow [CBF] <30%, volume: 26 mL; Tmax >6.0 seconds, volume: 145 mL). (D) Diffusion-weighted imaging showed a newly developed acute lesion in the basal ganglia and corona radiata.

ported by evidence derived from randomized clinical trials, as in our case. The authors admit that our aggressive therapeutic approaches (i.e., triple antiplatelet therapy and extended use of phenylephrine) are not supported by current stroke treatment guidelines. Given that the cerebral perfusion of the patient in the left MCA territory was mainly supplied via collateral circulation from the opposite side through the anterior communicating artery, newly developed proximal MCA occlusion could have led to extensive infarction in the left MCA territory. To prevent the ischemic penumbra from expanding, the authors believed that PIHT would serve as a viable option for augmenting cerebral perfusion to the ischemic penumbra. Whether sustaining PIHT for an extended period that far exceeds the previously recommended safe window is indeed an optimal decision may be controversial. However, prolonged PIHT beyond the conventional safe window was inevitable as his symptoms were highly dependent on the BP; therefore, PIHT was sustained until he became neurologically stable regardless of the BP.


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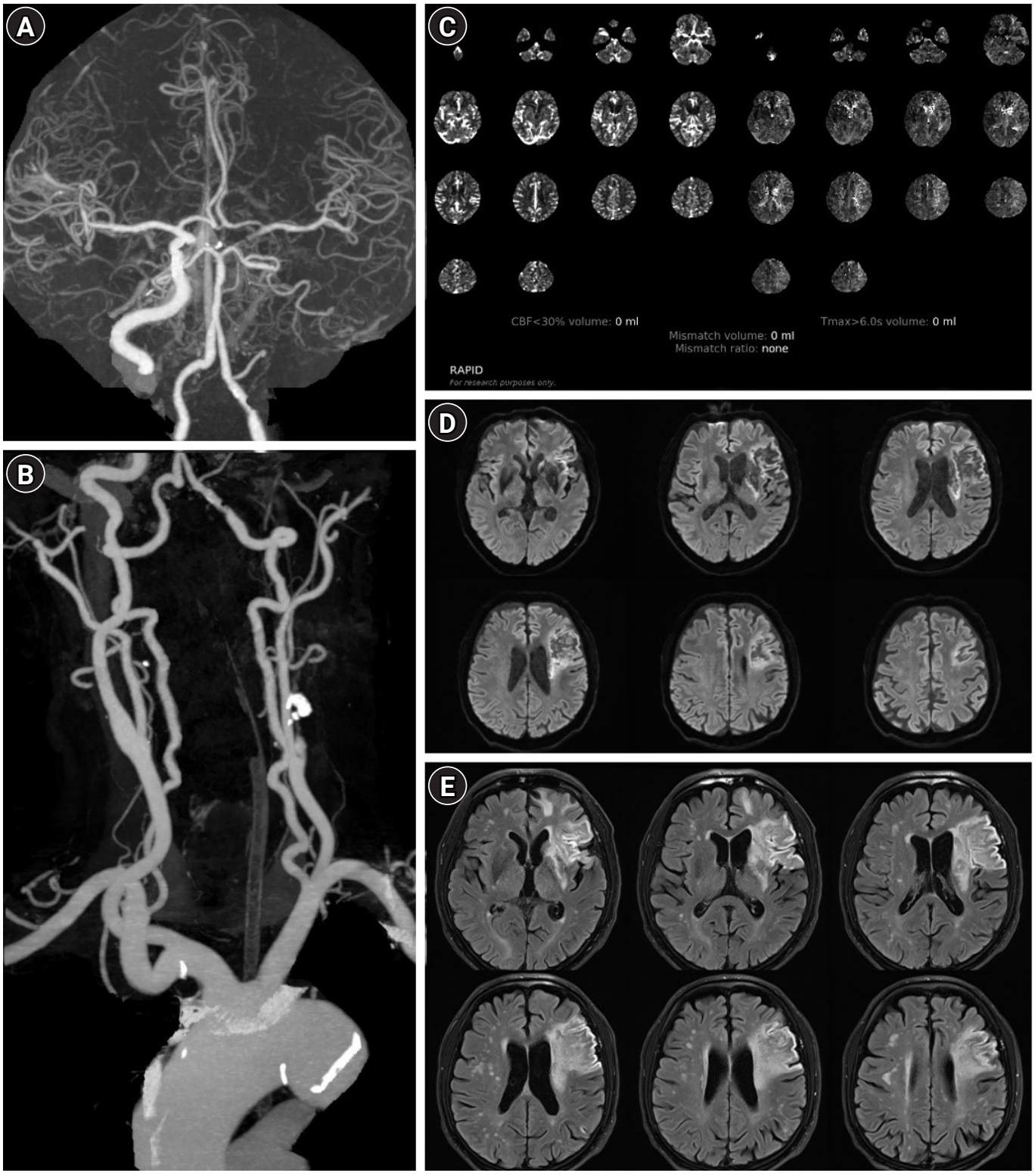


**Fig. 3.** Follow-up brain perfusion computed tomography angiography (CTA) and magnetic resonance imaging were performed on day 24 after early neurologic deterioration. (A) Brain CTA showed spontaneous recanalization of the left middle cerebral artery and (B) no interval change of the internal carotid artery occlusion. (C) Perfusion mismatch was no longer observed. (D, E) No new lesions were identified on diffusion-weighted imaging or fluid-attenuated inversion recovery. CBF, cerebral blood flow.

It has been recently reported that rescue mechanical thrombectomy improves the prognosis of acute neurological deterioration [9]. However, in that study, only three patients had neurological deterioration 24 hours after admission. As such, rescue thrombectomy could have been considered in our case; however, this was not supported by the treatment guidelines.

The recanalization of the MCA occlusion in our case was unexpected. Spontaneous recanalization of the occluded MCA has been reported to occur infrequently [10]. It is known to occur mainly in MCA occlusions due to cardiogenic embolism or dissection. Since digital subtraction angiography was not performed in our case, there is a limitation that we were unable to accurately determine the location of the initially occluded blood vessel. When neurologic deterioration occurs, the mechanism of MCA occlusion can be estimated as thrombus propagation or artery-to-artery embolism. According to a previous study [11], the location of the occluded blood vessel is likely to be the cavernous segment of the ICA, considering that the cervical occlusion was initially shaped like a spearhead and some flow of the cavernous portion was observed (Fig. 1). Although the mechanisms of thrombus propagation are not well known, it is known that stenosis or irregular vessel geometries affect blood flow velocity, which influences the function of the von Willebrand factor to cause thrombus formation and propagation [12].

In our case, as the BP dropped and collateral flow slowed, it was assumed that the thrombus, which was initially located in the cavernous segment, was propagated to induce occlusion of the proximal MCA. Considering that the shape of the cervical occlusion was transformed into a stump on CTA performed after neurological deterioration (Fig. 2), it is possible that a new thrombus was formed in the proximal ICA at this point, which flowed forward, thereby occluding the proximal MCA. Both mechanisms were based on atherosclerosis, and no cardioembolic source was identified in our patient. The mechanism of spontaneous recanalization of atherosclerotic occlusion is not clearly understood. Various mechanisms have been proposed to explain this mechanism [13]. Collateral circulation may facilitate fibrinolysis while compensating for the blood supply. Antiplatelet agents and statins inhibit platelet aggregation, reverse the formation of atherosclerotic plaques, and inhibit the focal inflammatory response, which may help establish spontaneous recanalization. Therefore, the authors' use of the three antiplatelet agents was possibly helpful. We surmise that the occluded vessel was recanalized spontaneously, and at the same time, prolonged PIHT played a role by sustaining the collateral flow, thereby preventing the penumbra from converting into the infarction core, stalling until delayed recanalization occurred.

In our case, if the patient's symptoms worsened despite PIHT, additional perfusion CT should be performed to evaluate the change in mismatch volume. If the worsening of cerebral perfusion was confirmed as a mismatch volume, bypass surgery would be the only treatment option since it was too late to perform an intra-arterial procedure. Fortunately, PIHT prevented further neurological deterioration, and this case highlights that prolonged PIHT may serve as a viable therapeutic option for managing END in patients ineligible for EVT. This report provides evidence that prolonged PIHT may be beneficial in certain cases and that the duration may be modified according to the neurological status unless the patient shows adverse effects on PIHT. Although our findings may not be completely generalizable to standard clinical practice, this case has clinical implications for managing patients who experience END without alternative treatment options.

## ARTICLE INFORMATION

### Ethics statement

This case was reviewed and approved by the Institutional Review Board of National Health Insurance Service Ilsan Hospital (IRB No. NHIMC 2021-11-007). The need for informed consent was waived by the Board.

### Conflict of interest

No potential conflict of interest relevant to this article.

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Conceptualization: HKN, JHK, KDS. Data curation: HKN, TW, JYY, WP, JK, SK. Formal analysis: HKN, KDS. Methodology: HKN, JK. Project administration: HKN, KDS. Visualization: HKN, KDS. Writing–original draft: HKN. Writing–review & editing: KDS.

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# A case of Brown-Sequard syndrome caused by spinal cord infarction

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IMAGES IN NEUROCRITICAL CARE

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Typical imaging hallmarks of spinal cord infarction include bilateral anterior or central cord lesions. However, unilateral hemicord lesions were rarely reported [1]. A 94-year-old woman visited our institution due to sudden right hemiplegia. Neurological examination findings were consistent with Brown-Sequard syndrome. The motor functions of the right arm and leg were given Medical Research Council scale grades of 1 and 2, respectively. Touch sensation was decreased in the right arm, trunk, and leg. Pain and temperature sensations were decreased on the left side.

Magnetic resonance imaging showed diffusion restriction and T2-hyperintensity of the spinal cord between C2 and C5 level (Fig. 1). Cerebral angiography revealed a right vertebral artery occlusion (Fig. 2). The ischemia of separated anterior spinal arteries or sulco-commissural arteries can provoke partial Brown-Sequard syndrome [2]. However, under the above conditions, posterior spinal artery territories remain spared.

The radiculomedullary arteries are branches of radicular arteries arising from the vertebral artery. They form a Y-shaped branch in the cervical region supplying both anterior and posterior spinal artery territories [3,4]. Ischemia of the unilateral radiculomedullary artery could provoke hemicord infarction [4]. In our case, occlusion of the right vertebral artery might have caused an ischemia of the ipsilateral radiculomedullary artery.

## ARTICLE INFORMATION

### Ethics statement

Ethical approval for this study was not needed in accordance with our Institutional Ethics Policy. This case report did not include any protected health information. Written informed consent was obtained from the patient.

### Conflict of interest

No potential conflict of interest relevant to this article.

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### Author contributions

Conceptualization: SYS. Data curation: KL. Formal analysis: SYK. Project administration: KL, SYK. Visualization: SYK. Writing–original draft: SYK. Writing–review & editing: all authors.

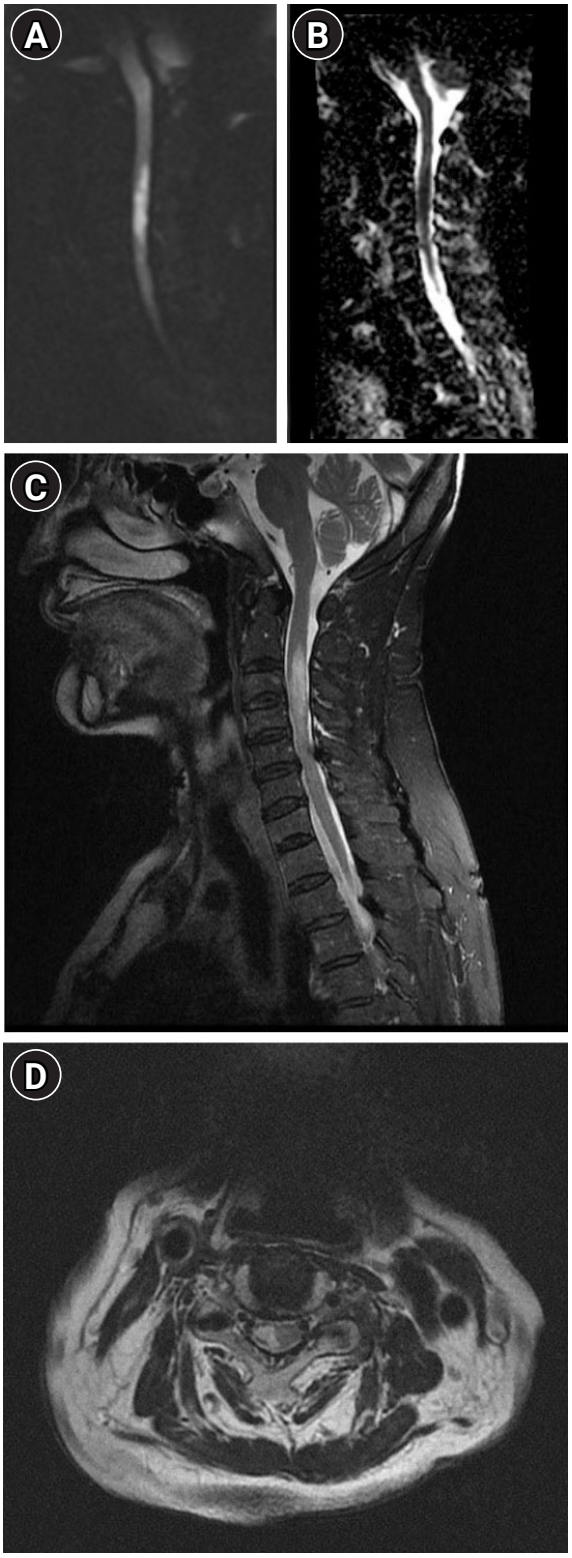


Fig. 1. Magnetic resonance imaging scans of cervical spinal cord obtained on admission date. (A, B) Diffusion-weighted imaging demonstrates diffusion restriction of the spinal cord between C2 and C5 level. (C) Sagittal T2-weighted image demonstrates high T2 signal intensity of the spinal cord between C2 and C5 level. (D) Axial T2-weighted image shows high T2 signal intensity of the right half of the spinal cord at C4 level.

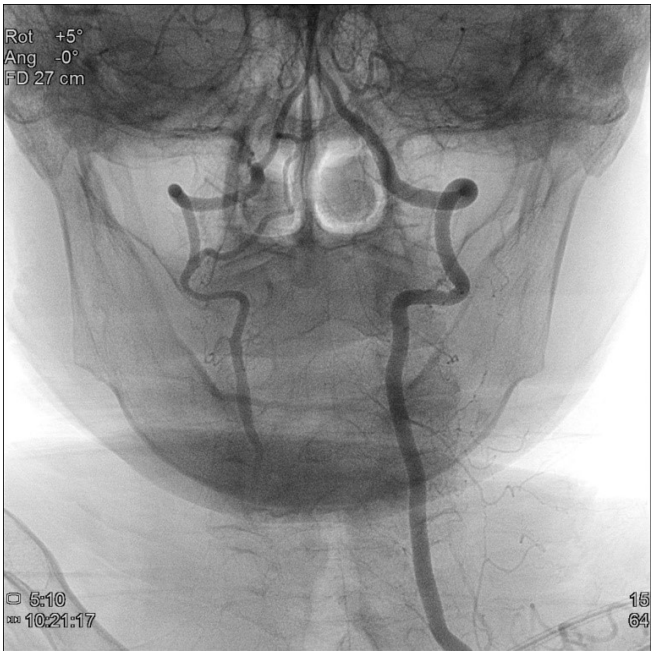


Fig. 2. Percutaneous cerebral angiography of posterior circulation showing the occlusion of right vertebral artery from its origin. The left vertebral artery, on the other hand, is intact.

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Journal of Neurocritical Care

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The revised instructions for authors will be applicable from September 2021.

**Revision History**

• Aug 2020

- Included a statement regarding IRB approval for case reports.

• Sep 2021

- Enhanced the description regarding institutional or ethical

approval and informed consent.
- Added details regarding requirement of the manuscripts to adhere to recognized reporting guidelines relevant to the research design used and to submit a checklist as part of the initial submission.

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As the corresponding author, I declare the following information regarding the specific conflicts of interest of authors of our aforementioned manuscript.

Examples of conflicts of interest include the following: source of funding, paid consultant to sponsor, study investigator funded by sponsor, employee of sponsor, board membership with sponsor, stockholder for mentioned product, any financial relationship to competitors of mentioned product, and others (please specify).

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