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Acute and Critical Care

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Regional scope: Its regional scope is mainly Asia, but it welcomes submissions from researchers all over the world.

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This work was supported by the Korean Federation of Science and Technology Societies Grant funded by the Korean Government (Ministry of Education).

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This journal is primarily intended for scientific researchers and personnel who work for acute, critical care. However, its readership can be expanded to other positions: students can understand recent trends in acute, critical and intensive care medicine; physicians can obtain recent topics and cases for continuing education; policy makers are able to reflect the results of the articles to nation-wide public health and science promotion policies.

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Title change and language

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Sex or gender differences in treatment outcomes of sepsis and septic shock

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Gender disparities in intensive care unit (ICU) treatment approaches and outcomes are evident. However, clinicians often pay little attention to the importance of biological sex and sociocultural gender in their treatment courses. Previous studies have reported that differences between sexes or genders can significantly affect the manifestation of diseases, diagnosis, clinicians' treatment decisions, scope of treatment, and treatment outcomes in the intensive care field. In addition, numerous reports have suggested that immunomodulatory effects of sex hormones and differences in gene expression from X chromosomes between genders might play a significant role in treatment outcomes of various diseases. However, results from clinical studies are conflicting. Recently, the need for customized treatment based on physical, physiological, and genetic differences between females and males and sociocultural characteristics of society have been increasingly emphasized. However, interest in and research into this field are remarkably lacking in Asian countries, including South Korea. Through this review, we hope to enhance our awareness of the importance of sex and gender in intensive care treatment and research by briefly summarizing several principal issues, mainly focusing on sex and sex hormone-based outcomes in patients admitted to the ICU with sepsis and septic shock.

Key Words: intensive care units; sepsis; septic shock; sex

INTRODUCTION

Sex and gender are essential in epidemiologic data in almost all clinical research papers. However, most clinicians ignore the distinction between these two terms and often pay little attention to the clinical importance of sex and gender when they treat patients. Sex is a term that describes biological differences between sexes, reflecting sex chromosomes, sex hormones, and anatomical structures between males and females and resulting differences in physiological characteristics, while gender is a term that reflects sociocultural factors, such as differences in gender identity (man and woman, boy and girl), societal roles and status, and behavioral patterns of genders [1]. With a sociocultural base, gender reflects differences in gender-specific medical demand, accessibility to medical services, and service provision methods [2].

Previous studies have reported that biological and sociocultural differences between males and females can significantly affect the diagnosis of diseases, clinicians' decisions about treat-

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ment, scope of treatment, and the incidence and manifestations of disease [3,4]. In the intensive care field, it has been reported that the complex interaction between sex and gender has a significant impact on disease manifestations, treatment responses, and patient outcomes [3]. While most studies on sex or gender differences in disease presentation and treatment behaviors in intensive care units (ICUs) have been conducted in western countries, studies conducted in Asian countries with a Confucian culture, such as South Korea, are scarce. However, as the demand for customized treatment based on individual characteristics increases, researchers and clinicians are paying more attention to sex and gender as essential variables. Reflecting this, in 2016, the United States National Institutes of Health (US NIH) recommended that sex be included as an essential biological variable in all animal or cell research [5,6]. The Canadian Institutes of Health Research also published guidelines emphasizing the importance of sex and gender in biomedical research [1].

Male sex is a well-known possible risk factor for sepsis and septic shock. Sepsis is more prevalent in men than in women, showing an annual relative risk of 1.3 times that of women [7]. In addition, among septic shock patients admitted to ICUs, males were more prevalent than females. Men also showed longer length of ICU stay, longer duration of hospitalization, higher ICU mortality, higher likelihood of readmission within 90 days and 1 year, and more frequent death at 1 year after the event of sepsis [8,9]. Although the possible mechanism explaining sex difference in manifestation of sepsis remains unclear, beneficial roles of many genes and their products expressed from a silent X chromosome in women and sex hormones such as estrogen in the regulation of immune responses in sepsis have been suggested [10,11].

Through this review, we hope to enhance awareness of the importance of sex and gender in intensive care treatment and research by briefly summarizing principal issues, mainly focusing on sex and sex hormone-based differences in treatment outcomes of patients admitted to the ICU with sepsis and septic shock.

THE ROLE OF ESTROGEN IN REGULATING INFLAMMATORY RESPONSE

Estrogen is a sex hormone that regulates the development and function of the female reproductive system. Before menopause, estrogen is mainly synthesized in the ovaries. After menopause, it is produced in adipose tissues (breasts), brain, kidneys, liver, and bones [12]. In men, estrogen is produced primarily in

KEY MESSAGES

- As the demand for customized treatment based on individual characteristics increases, researchers and clinicians should increase their awareness of the critical role of biological sex and sociocultural gender.
- Although the possible mechanism explaining sex-different manifestations and outcomes of sepsis remains unclear, the beneficial roles of gene expression from a silent X chromosome and sex hormones in regulating immune responses in sepsis have been suggested.
- Future research targeting intensive care unit care must reflect characteristics of biological sex and sociocultural gender based on sociocultural background.

the testes. The proportion of estrogen produced in secondary tissues is relatively higher in men than in women [13]. Among four types of estrogens (estrone, estradiol, estriol, and etestrol), estradiol is the most potent. It can bind to estrogen receptors in the nucleus, plasma membrane, and endoplasmic reticulum and exert its functions through genomic and non-genomic mechanisms [14,15]. There are currently three known estrogen receptors: estrogen receptor alpha (ERα), estrogen receptor beta (ERβ), and guanine nucleotide-binding protein-coupled estrogen receptor 1 (CPER1/CPR30) [16]. Estradiol participates in the regulation of proinflammatory signaling/pathways in the immune system. It acts mainly as an anti-inflammatory agent through ERα and CPER1 [17,18] and has various anti-inflammatory and proinflammatory functions through ERβ [19,20]. Diverse effects of estrogen on inflammation are believed to be due to various expression levels of estrogen receptor based on cell type and physiological state [21].

DIFFERENT EFFECTS OF SEX HORMONES ON THE OUTCOMES OF SEPSIS IN ANIMAL STUDIES

Protective Effects of Estrogen Against Sepsis

Evidence supporting the protective effects of estrogen has been accumulating for several decades. Most of these data are associated with dampening the hyperinflammatory state of sepsis by reducing expression levels of circulating proinflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α [21].

Experiments using proestrus female mice in a cecal ligation sepsis model demonstrated that immune functions of preserved splenocytes are associated with better survival [22].

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Addition of 17β-estradiol to splenocytes from ovariectomized female mice normalized immune functional capacities in a trauma-hemorrhage model [23]. Another study performed with a mouse model of hemorrhage and subsequent sepsis showed a greater increase in plasma proinflammatory cytokines including IL-6, TNF-α, and prostaglandin E2 in male mice than proestrus female mice. They also showed a survival advantage of female sex hormones against subsequent septic challenge [24]. In addition, less pronounced cardiac dysfunction was seen in female mice than in male mice in a cecal ligation and puncture (CLP) sepsis model [25]. In that study, female mice showed decreased production of TNF-α, IL-6, and inducible nitric oxide synthase. Cardioprotective effects were shown in ovariectomized female mice after administration of landiolol in a CLP sepsis model. Such effects were assumed to be due to overexpression of genes involved in calcium influx. In contrast, inactivation of the β-adrenergic and a calcium efflux pathway was seen in control females [25]. The protective effect of estrogen against liver damage in sepsis has also been observed in a lipopolysaccharide (LPS)-induced sepsis model. Female septic mice showed liver damage with increased serum aspartate aminotransferase and alanine aminotransferase levels as well as extensive necrosis, and both were more severe in male septic mice. In addition, ovariectomy-aggravated sepsis-induced liver damage and activation of the pyroptosis signaling pathway could be alleviated by estrogen [26].

Suppressive Effects of Testosterone on the Immune System in Sepsis

Sex-dependent differences in the incidence and severity of sepsis make males more susceptible to septic shock than females. Testosterone is a primary male sex hormone and has also been implicated in sex-dependent differences in sepsis. Testosterone has significant immunosuppressive effects on innate and adaptive immunity by reducing immunoglobulin, cytokine production, and lymphocyte proliferation [27,28]. LPS-induced TNF-α secretion in plasma was significantly enhanced in rats receiving neonatal androgen blockade with flutamide and in prepubertal orchiectomies rats, suggesting testosterone's immunosuppressive role in inflammation [29]. Another study showed that orchiectomized mice were significantly more susceptible to endotoxic shock, and that macrophages isolated from them had significantly higher toll-like receptor-4 cell surface expression than those derived from sham gonadectomized mice. However, these effects were dampened in orchiectomized mice receiving exogenous testosterone [30]. Although the details of the under-

lying molecular mechanisms remain unclear, effects of androgen receptor blockade are thought to be partly attributable to the upregulation of estrogen receptors or enhanced estrogen receptor-related pathways [31-33].

SEX DIFFRENCE IN MANIFESTATIONS AND OUTCOMES OF SEPSIS IN HUMAN STUDIES

Epidemiologic Differences Based on Sex

A higher prevalence of sepsis in men than in women has been reported in various nationwide or individual hospital-based epidemiologic studies [34]. A longitudinal, population-based epidemiological study of sepsis from 2005 to 2012 using the Korean National Health Insurance Service-National Sample Cohort—a population-based cohort representing 2.2% of the Korean population—reported that 53.5% to 58.0% of a total of 22,882 sepsis cases were males. It also found that female sex was an independent favorable risk factor for 6-month mortality in multivariate logistic regression analysis, showing an odds ratio (OR) of 0.7 (95% confidence interval [CI], 0.66–0.76; P<0.001) [35]. Potential mechanisms explaining the higher prevalence of sepsis in men are unclear. However, the combination of biological sex differences, such as the immune system, sex hormones, gene expression from a silent X-chromosome, anatomical differences, and pharmacokinetics and dynamics for drugs [10,11,36,37], and sociocultural gender differences in disease perception, risk behavior, accessibility to and use of healthcare resources, and service provision methods are thought to play a critical role in sex disparities in sepsis [38-40].

Sex Preference in the Source of Bacterial Infections

Sexual differences in bacterial infections have been reported in human and animal models. Diverse manifestations and outcomes of infections based on sex are intricately linked to genetic, biological, and behavioral differences, which are associated with gender preferences of specific bacterial infections, sex hormones, and immune responses by sex [41,42]. In general, men are more susceptible to gastrointestinal and respiratory bacterial diseases and sepsis, while women are more susceptible to genitourinary tract infections [43]. Recent studies have reported that tissue-specific expression of sex hormone receptors contributes to the sexual disparity in bacterial infections [43]. According to a prospective observational study on community-acquired severe sepsis and septic shock conducted in 12 university hospitals in South Korea, among a total of 1,192 patients, gastrointestinal (26.8% vs. 20.9%), respiratory (39.2%

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vs. 19.2%), and skin and soft tissue (11.0% vs. 4.7%) infections as a source of primary infection were higher in men (men vs. women), while urinary tract infection (11.4% vs. 44.8%) was more prevalent in women (P<0.05 for each) [44].

Sex Differences in Outcomes of Sepsis and Septic Shock

Numerous individual and nationwide studies have evaluated the relationship between sex and mortality from sepsis and septic shock. However, evidence showing an association of sepsis mortality with specific sex is conflicting. Although preclinical studies have suggested potential protective effects of estrogen on sepsis, some studies have shown higher mortality rates in women with sepsis [45-48]. In comparison, others have shown higher mortality rates in men with sepsis [49-51]. Furthermore, some studies have reported no difference in mortality rate from sepsis and septic shock between sexes [52-54]. According to a recently published meta-analysis including 13 studies with 80,520 participants, there were no sex-based differences in all-cause hospital mortality (OR, 1.02; 95% CI, 0.79–1.32; very low-certainty evidence) or all-cause ICU mortality (OR, 1.19; 95% CI, 0.79–1.78; very low-certainty evidence). Interestingly, however, females presented higher 28-day all-cause mortality (OR, 1.18; 95% CI, 1.05–1.32; very low-certainty evidence) and lower 1-year all-cause mortality (OR, 0.83; 95% CI, 0.68–0.98; low-certainty evidence) [55]. An epidemiologic study for severe community-acquired sepsis and septic shock conducted in South Korea reported that 28-day mortality (27.0% vs. 18.1%), in-hospital mortality (32.9% vs. 22.0%), and sepsis-related mortality (28.3% vs. 18.1%) were lower in females (P<0.001 for each) [44]. Several explanations have been suggested for these disparate findings in clinical studies of sex differences in sepsis and septic shock. The most critical issues were heterogeneous study designs (prospective vs. retrospective, single vs, multi-center or nationwide database), different definitions of sepsis, different baseline health statuses, comorbidities, severity of sepsis, age, and sociocultural differences affecting treatment attitudes for men and women [56]. Among these, age is a critical factor to consider when assessing the protective effects of estrogen against sepsis. Level of estradiol, the most potent estrogen, is highest in women between prepuberty and menopause. In contrast, the prevalence of sepsis and septic shock is significantly higher in patients over 60 years of age. Multiple comorbidities are also more common in these patients. Thus, when evaluating effects of sex factors on outcomes of sepsis, age stratification and control of confounding factors such as comorbidities should be considered [56]. In a study conducted

on 143 polytraumatized patients with injury severity score >16 and between 16 and 65 years old, the prevalence of multiorgan dysfunction syndrome and sepsis was significantly lower in females younger than 50 years with an injury severity score >25 than in age-matched males [57]. However, when focusing on clinical studies specifically examining sex hormones in connection to sepsis patients, results are again conflicting. Higher circulating estradiol levels were associated with higher mortality rates in both male and female patients, and elevated serum estradiol levels were associated with the severity of renal dysfunction and the development of acute kidney injury [58-60]. In addition, while levels of proinflammatory cytokines such as TNF-α and IL-6 were increased in male patients, anti-inflammatory cytokine IL-10, which was defined as a predictor for the severity of sepsis, was higher in female patients [28,61,62]. Thus, differences in study conclusions might be attributed to differences in sex steroid levels among patients rather than a difference in the type of sex hormones alone.

GENDER DISPARITIES IN MEDICAL TREATMENT IN THE ICU

Many studies have reported that treatment opportunities in the ICU differ depending on gender. Most studies have pointed out that women have a lower tendency to receive advanced life-supporting measures, including early goal-directed treatment for sepsis, mechanical ventilatory support, renal replacement therapy, and other invasive procedures [63,64]. Pharmacokinetic and pharmacodynamic differences between male and female patients have also recently attracted attention from clinicians. Adverse events from medications used in the ICU were more prevalent in female patients.

Possible explanations include sex-associated anatomic and physiologic factors, such as lower body weight, higher proportion of fat compared with muscle, and lower plasma volume, which can easily lead to an over-concentration of medicine and toxicity in females [38]. However, considering different physical traits between western and Asian women and the differences in sociocultural attitudes toward female gender between western and Asian countries, gender differences in ICU treatment should be individually evaluated and interpreted based on each country's sociocultural background.

CONCLUSIONS

Many studies have reported that sex or gender differences

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can affect the perception and manifestation of the disease, treatment decision, response to treatment, and outcomes in patients admitted to the ICU. Among them, the immunomodulating effects of sex hormones and differences in sex-specific gene expression potentially play an important role in treatment outcomes of sepsis and organ dysfunction in animal studies. However, results in human studies are conflicting. In clinical research, sex or gender differences in outcomes of sepsis patients are further confused by the differences in diagnosis and treatment provision depending on sociocultural background. Even if the need for customized treatment based on an individual's characteristics has been increasingly emphasized based on physical, physiological, and genetic differences between women and men at a time when sociocultural considerations are necessary, interest and research in this field are remarkably lacking in Asian countries, including South Korea. Therefore, future research targeting septic patients in the ICU is needed to reflect characteristics of biological sex and sociocultural gender based on sociocultural background.

CONFLICT OF INTEREST

Dohhyung Kim is an editorial board member of the journal but 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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Conceptualization: DK. Data curation: HJY. Writing–original draft: SYM, HJY. Writing–review & editing: DK.

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Microbial infections in burn patients

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Polymicrobial infections are the leading causes of complications incurred from injuries that burn patients develop. Such patients admitted to the hospital have a high risk of developing hospital-acquired infections, with longer patient stays leading to increased chances of acquiring such drug-resistant infections. *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Proteus mirabilis* are the most common multidrug-resistant (MDR) Gram-negative bacteria identified in burn wound infections (BWIs). BWIs caused by viruses, like herpes simplex and varicella zoster, and fungi-like *Candida* species appear to occur occasionally. However, the preponderance of infection by opportunistic pathogens is very high in burn patients. Variations in the causative agents of BWIs are due to differences in geographic location and infection control measures. Overall, burn injuries are characterized by elevated serum cytokine levels, systemic immune response, and immunosuppression. Hence, early detection and treatment can accelerate the wound-healing process and reduce the risk of further infections at the site of injury. A multidisciplinary collaboration between burn surgeons and infectious disease specialists is also needed to properly monitor antibiotic resistance in BWI pathogens, help check the super-spread of MDR pathogens, and improve treatment outcomes as a result.

Key Words: burn wound infections; biofilm; epidermis; hospital; opportunistic infection

INTRODUCTION

The human skin is the largest anatomical organ involved in various physiological functions like thermoregulation, maintaining homeostasis, proprioception, and protection from external agents [1]. The skin is man's physical barrier to resist pathogen attack. Conditions that lead to loss of skin integrity therefore have numerous serious consequences [1].

BURN INJURIES

Burn injury is a major global public health crisis. It disrupts the epidermal barrier, leading to down-regulation of both local and systemic immune responses [1]. As a result, burn wounds become an ideal breeding ground for microbes [1,2]. The burn wound serves as an ideal microenvironment predominated with biological fluids called burn wound exudates (BWEs), which collectively create a perfect niche for the growth of pathogens [3].

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First-degree (superficial) burns damage only the epidermal layer, so they heal rather quickly without scarring [2]. Second-degree (partial-thickness) burns involve the deeper layers of the epidermis and dermis and heal slowly [2]. Third-degree (full-thickness) burns fully destroy the epidermal and dermal layers of the skin and can also cause significant damage to the underlying tissues and bones as well [2].

EPIDEMIOLOGY OF BURN INJURIES

Burn is a very common and devastating form of trauma. It has been ranked seventh among all traumatic injuries by the World Health Organization, with a crude mortality rate of 5% [4]. Across the world, around 2.65 lakh deaths occur every year due to burn injuries. Such cases are more prevalent in developing and under-developed countries, and in these cases, patient mortality potential soars up to 100% with burns covering more than 40% of the total body surface area [3,5]. Around 80% of burns occur at home [6]. Domestic burn injuries are more common among children and adolescents [6,7].

Asia records the highest number of intentional burn injuries in the world, with Southeast Asia topping the list, followed by Africa [8]. Among the Asian countries, India records the highest number of cases of intentional self-harm by burning, followed by Pakistan, Bhutan, and Bangladesh. Africa records the highest mortality rate from burn injuries, 23.5% per year [8]. In India, 65% of the burn victims are young women, due to self-immolation or domestic violence [9]. On the other hand, in Africa, children are the predominant victims of burn injuries. Prevention of burn injuries in Asia and Africa is hampered due to the high population density, lack of education, low income rate, and poor surveillance systems [9].

Reported cases of burn injuries are significantly lower in continents like North America, South America, Australia, and Europe [8]. The victims of intentional self-harm by burning in Europe are more prevalent among men in the age group of 40–50 years [9]. Australia records the highest number of admissions of burn patients in hospitals each year, followed by Asia. These developed continents are in a much better situation concerning burn injuries compared to the under-developed and developing countries. Polymicrobial infections are responsible for 75% of all deaths from burns [2]. The risk factors influencing microbial infections at the burn site include the size and surface area of the burn, age, immune status, the degree of burn, and comorbidities [2].

KEY MESSAGES

- The loss of skin epidermis due to burn injury provides easy access for different microorganisms to enter the human body and cause infections.
- Most of the complications related to burn injuries that are reported occur due to the increased susceptibility to several other secondary diseases caused by microbial infections.
- Multidrug-resistant bacterial, yeast, fungal, and viral infections of burn wounds are very common during prolonged hospitalization, and immunosuppression is the main cause.

ETIOLOGY OF BURN INJURIES

Burns occur at temperatures above 44 °C [10]. Trans-epidermal necrosis happens in just a second at 70 °C, while it happens in 45 minutes at 47 °C [10]. Fire flaming and scalding represent 23.8% and 66.2% of burn injury cases, respectively [11]. The remaining 10% of burns have other causes [11]. Scalding causes first or second-degree burns, while flame causes second or third-degree burns [10].

Burns are grouped as thermal, chemical, frostbite, electrical, radiation, or sunburn [10]. Around 3%–6% of all burn cases constitute chemical burns, accounting for 14%–30% of mortalities [10]. Chemical burns develop due to contact with coal tar, strong acids, alkaline solutions, or phosphorus due to bomb explosions [10]. Cold burn or frostbite occurs as the skin starts freezing from –10 °C, with irreversible changes occurring below –22 °C [10].

PATHOGENS OF BURN WOUND INFECTIONS

Following burns, microorganisms colonize and grow quickly at the site of injury due to the loss of the skin barrier. The skin barrier otherwise serves as the first line of immune defense for any individual [12-14]. Any breach in the skin allows for easy entry and access of the infecting microbe to the inner tissues of the body, thus complicating the etiology [12-14]. Hence, it has been observed that microbial infections, especially those caused by multidrug-resistant (MDR)-bacteria, including *Pseudomonas* and *Acinetobacter*, are the main cause of increased morbidity and mortality in burn patients [12-14].

The 2016 National Burn Repository Report mentioned that

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seven out of ten most frequent complications in burn patients are attributed to polymicrobial burn wound infections (BWIs), with urinary tract infections (UTIs), pneumonia, and cellulitis topping the list and respiratory tract infections being the most frequently reported [13]. After a burn injury, the duration of hospitalization is directly proportional to the types of bacterial species that infect the patients, with the major contributor to infection being *Staphylococcus aureus* (Figure 1, Table 1) [15]. During the first week of hospitalization, skin and soft tissue infections occur majorly, whereas pneumonia, UTIs, and bloodstream infections tend to occur later during the stay (Table 2) [15].

Gram–Positive Bacteria

The most commonly found Gram-positive bacteria in BWI include *Staphylococcus* species (spp.), *Enterococcus* spp., and β-hemolytic group A *Streptococci* (GAS) [12]. Specifically, vancomycin-resistant *Enterococci* (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA) are the pathogens of high concern in patients with severe burns [12,13]. Over recent decades and with the uncontrolled over-the-counter availability of broad-spectrum antibiotics, MRSA has become the most pre-

dominant pathogen in the intensive care unit of burn patients [14]. Colonization with any of these bacteria may also lead to biofilm infections, resulting in severe illness and death [14].

In most of the studies performed so far, about 86.6% of *S. aureus* found were methicillin-resistant, a major pathogen of hospital-acquired infections (HAIs) in most countries [16]. The toxic products proceeding *Staphylococcus* spp. infection,

Table 1. Bacterial pathogens isolated from burn wound infections

Bacterial pathogens	Percentage of occurrence (%)
Citrobacter freundii	0.77
Escherichia coli	8.46
Klebsiella pneumoniae	13.85
Proteus mirabilis	4.62
Proteus morganii	0.77
Staphylococcus aureus	33.85
Staphylococcus epidermis	3.85
Pseudomonas putida	3.08
Pseudomonas aeruginosa	15.38
Acinetobacter baumannii	15.38

Adapted from El Hamzaoui et al. New Microbes New Infect 2020;38:100764 [15].
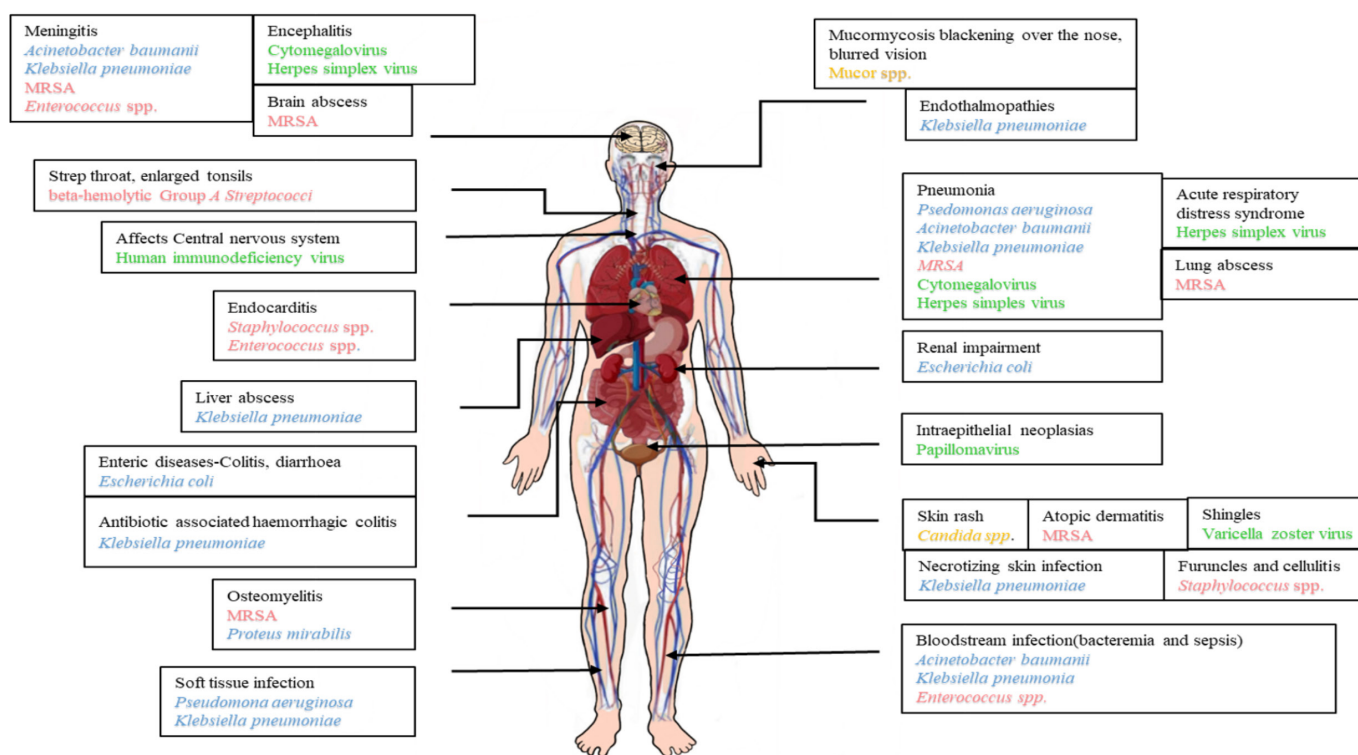
Figure 1. Burn wound infection microbes and their effect on a burn patient. MRSA: methicillin–resistant *Staphylococcus aureus*; spp.: species.

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Table 2. Categories and effects of different pathogens causing burn wound infections

Category of microorganisms	Microorganisms responsible for causing burn wound infections	Prevalence and severity of microorganisms	Effect of the microorganism on burn patients
Gram positive bacteria	*Staphylococcus* spp.	Most common	They cause infection which encompasses causes skin lesions like furuncles, and cellulitis; and sometimes pneumonia, endocarditis, and osteomyelitis, along with biofilm formation.
	β-Hemolytic group A *Streptococcus*	Common	They cause strep throat, enlarged lymph nodes in the neck, enlarged tonsils and rash.
	Enterococcus spp.	Common	They cause bacteremia, and infective endocarditis, UTIs, meningitis, and rarely causes intra-abdominal infections.
Gram negative bacteria	*Acinetobacter baumannii*	Most common, dangerous	It causes diseases such as pneumonia and meningitis, bloodstream infections (bacteremia and sepsis), delays in wound healing, graft losses, UTIs.
	Klebsiella pneumoniae	Most common	It causes endophthalmitis, pyrogenic liver abscess, splenic abscess, necrotizing skin infection, soft tissue infection, meningitis, antibiotic-associated hemorrhagic colitis, bacteremia, pneumonia, Lemierre syndrome.
	Pseudomonas aeruginosa	Most common, concerning	It causes infections in the blood, lungs (pneumonia), soft tissue infection, UTIs.
	Escherichia coli	Common	It causes enteric diseases, such as diarrhoea/dysentery, colitis, meningitis, low grade fever, vomiting, renal impairment.
Multidrug resistant bacteria	*P. aeruginosa*	Most common, dangerous	It causes infections in the blood, lungs (pneumonia), soft tissue infection, UTIs.
	A. baumannii	Most common	It causes diseases such as pneumonia and meningitis, bloodstream infections (bacteremia and sepsis), delays in wound healing, graft losses, UTIs.
	Klebsiella pneumoniae	Most common, concerning	It causes endophthalmitis, pyrogenic liver abscess, splenic abscess, necrotizing skin infection, soft tissue infection, meningitis, antibiotic-associated hemorrhagic colitis, bacteremia, pneumonia, Lemierre syndrome.
	Methicillin-resistant *Staphylococcus aureus*	Common, dangerous	MRSA causes skin infections like atopic dermatitis, followed by invasive infections like osteomyelitis, meningitis, lung abscess, pneumonia, brain abscess and central nervous system infection.
	Escherichia coli	Common	It causes enteric diseases, such as diarrhoea/dysentery, colitis, meningitis, low grade fever, vomiting, renal impairment.
	Proteus mirabilis	Common	It mostly causes UTIs, along with meningoencephalitis, empyema, and osteomyelitis.
Fungi	*Candida* spp.	Most common	They cause intense itching. Symptoms also include red, growing skin rash, rash on the skin folds, genitals, middle of the body, buttocks, under the breasts, and other areas of skin.
	Aspergillus fumigatus	Most common	It causes infections usually in people who have weakened immune systems.
	Saccharomyces boulardii	Uncommon	It causes fungemia.
	Mucor spp.	Uncommon, dangerous	They cause mucormycosis; fatal.
Viruses	Herpes simplex virus	Most common, very dangerous	It affects production of antibodies, cytokines, T-cells, IL-2, etc. Reactivation of the virus causes acute respiratory distress syndrome, pneumonia, liver necrosis, and encephalitis.
	Cytomegalovirus	Most common, very dangerous	It increases production of cytokines and causes hyperactivity of T helper cells and macrophages. It leads to organ dysfunction, pneumonia, encephalitis, and colitis.
	Varicella zoster virus	Common, dangerous	It causes shingles; post-herpetic neuralgia and delayed healing.
	Poxvirus	Rare	It causes formation of lesions and scabs.
	Human immunodeficiency virus	Rare	It decreases population of CD4$^+$ T-cells. It eventually leads to chronic multi-organ diseases and severe impairments within the central nervous system.
	Papillomavirus	Rare	It causes intraepithelial neoplasias.

spp.: species; UTI: urinary tract infection; MRSA: Methicillin-resistant *Staphylococcus aureus*; IL: interleukin.

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such as proteinases, collagenases, and hyaluronidases, allow the bacteria to enter local tissues and the bloodstream, which in turn cause generalized systemic infection and sepsis [14]. In addition to causing pneumonia, sepsis, and other sequelae related to invasive BWIs, Staphylococci are a significant cause of graft loss when the burden of infective organisms exceeds 10^5 colony-forming units (CFUs) [17]. Vancomycin has been one of the most preferred treatments for curbing MRSA infection. Yet for the past few years, there has been an emergence of other antibiotic-resistant strains like Vancomycin-intermediate *Staphylococcus aureus* [16]. A potential solution to this problem is being catered to by new antimicrobials such as linezolid (an oxazolidinone), daptomycin, tigecycline, quinupristin-dalfopristin, and dalbavancin [14].

Enterococcus also has been a Gram-positive bacterium of concern but fortunately was not seen to be fatal until the emergence of VRE [18]. Combination therapy, including ampicillin and an aminoglycoside, is nowadays used to treat VRE infections [18]. GAS (*Streptococcus pyogenes*) is the major cause of graft failure in burn patients, followed by group B Streptococci (*Streptococcus agalactiae*) [17]. These *Streptococci* can be eradicated with the penicillin group of antibiotics [19].

Gram–Negative Bacteria

P. aeruginosa are not only the major pathogens that cause respiratory tract infections (HAIs) but are also ubiquitous in invasive burn wounds, owing to their preference for moist environments [20]. These bacteria are also responsible for sepsis, leading to burn-associated death [20]. *Pseudomonas* infections, particularly those by *P. aeruginosa*, usually start as a localized, superficial lesion with a typical characteristic yellow or green color and a malodorous fruity smell, which may become an invasive infection termed "ecthyma gangrenosum," causing blue-purplish "punched-out" lesions in the skin [21]. *P. aeruginosa* can subsequently spread into deeper tissues rapidly to cause sepsis [22]. Because of the developing drug resistance patterns in *P. aeruginosa*, piperacillin-tazobactam combination therapy is administered. Aztreonam is used as an alternate therapy for MDR-*P. aeruginosa* [22].

The Gram-negative bacterium seconding the list of high-concern microbes in burn patients is *A. baumannii* because of their enhanced capacity for transfer between patients. Survivability in both wet and dry conditions, also on both inanimate and animate objects, helps them to achieve this. [23]. Colistin has been developed as the fallback treatment for pan-resistant *Acinetobacter* spp. [23].

The failure of burn treatment regimens is mostly caused due to the formation of a biofilm in the burn wound microenvironment of a patient; this may lead to death in many complicated cases [24]. The bacterial community encased within a polysaccharide matrix biofilm is more resistant to disinfection, the rigors of the host immune system, and critically, more tolerant to antibiotics [22]. It is assumed that burn wound-associated biofilms act as a launch pad for the pathogenic bacteria to establish deeper, systemic infections, and ultimately bacteremia and sepsis (Figure 2) [24]. Bacteria of the genera *Pseudomonas*, *Acinetobacter*, and *Staphylococcus* usually adopt a biofilm-encased mode of growth, with *P. aeruginosa* being the most common (33.3%) burn wound isolate with biofilm-forming abilities, followed by *Acinetobacter* spp. (23.3%) and *Staphylococcus aureus* (16.6%) [25,26].

MDR Bacteria

Antibiotics are used as a prophylactic measure to treat burn patients [27]. According to the European Centre for Disease Prevention and Control and the Centers for Disease Control and Prevention, among the drug-resistant (DR) bacteria, there are extensively drug-resistant strains that are resistant to at least one agent in all antimicrobial categories except a few, and pan-drug resistant strains, which are resistant to all agents under all antimicrobial categories [28,29].

Two principal factors that govern MDR-pathogen attacks are the severity and extent of the burn and the duration of hospital stay of the patient [30]. A prolonged hospital stay increases the risk of MDR infections by mostly Gram-negative bacteria (GNB) [30,31]. Further increases in such BWIs might be due to previous exposure to antibiotics, and the use of invasive medical devices like urinary catheters [30]. This was supported by a Canadian Burn Center study, where 125 patients were admitted [32]. Over the first 7 days, 6% of bacterial isolates were MDR, whereas after 28 days of hospital stay, it increased to 44% [32]. This increase in the prevalence of MDR-GNB during long hospital stays of burn patients is thus a serious treatment challenge [33].

Some of the most concerning MDR-GNB strains are *A. baumannii*, *Stenotrophomonas maltophilia*, *P. aeruginosa*, and carbapenem-resistant members of the Enterobacteriaceae family. These, along with *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Escherichia coli* are regarded as the most common MDR-GNB in BWIs [33,34].

In a study conducted at a burn unit of a tertiary care referral center located in North India, it was noted that MRSA and GAS
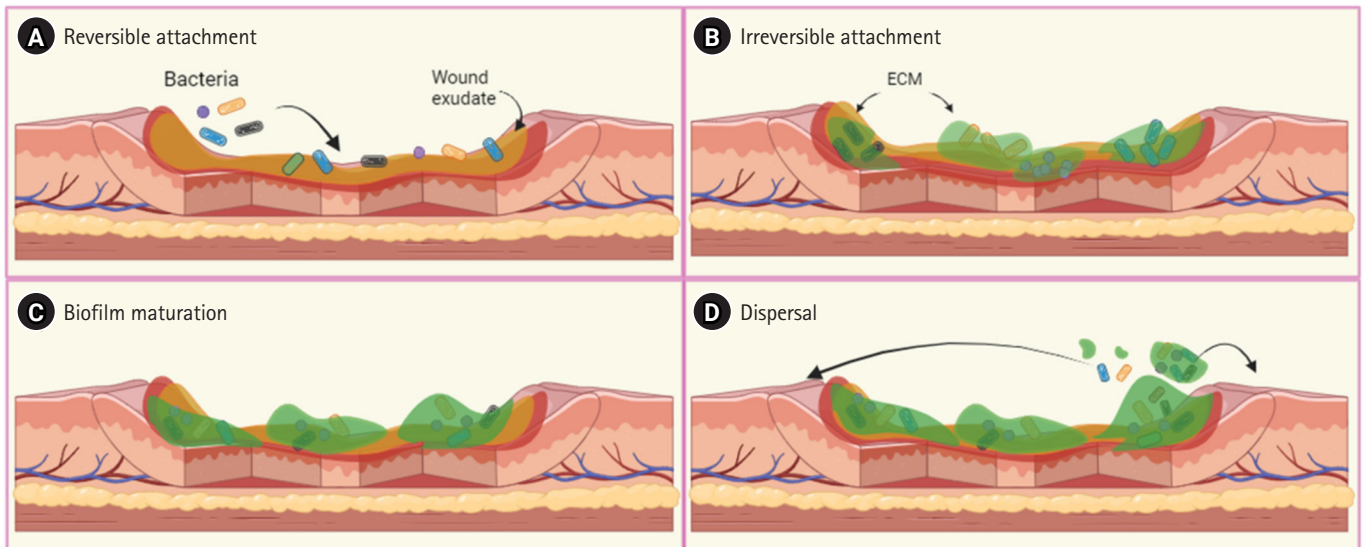
Figure 2. (A) Burn wounds typically contain burn wound exudates, which facilitate the initial inoculation and reversible attachment by bacterial pathogens. (B) Bacteria begin to produce extracellular matrix (ECM) and form micro-colonies during the process of irreversible attachment. (C) During the maturation stage, the biofilm grows in size and structural complexity. (D) The mature biofilm enters the dispersal stage, releasing bacterial cells from the ECM, which can then colonize new sites within the wound. Adapted from Maslova et al. NPJ Biofilms Microbiomes 2021;7:73 [3].

were endemic, where MRSA strains were reported to exhibit resistance to erythromycin, ciprofloxacin, netilmicin, gentamicin, and cefotaxime [35]. MDR *P. aeruginosa* was also one of the most frequent microbes cultured from the infected burn wounds there, and 90% of those displayed resistance to amikacin and ceftazidime [35].

The preliminary identification of these MDR pathogens is done by studying their physical morphology, Gram-staining properties, and biochemical characteristics [36]. Along with this, antimicrobial susceptibility tests are carried out using various antibiotics, like ciprofloxacin, gentamicin, trimethoprim-sulfamethoxazole, ceftazidime, and others, to check for the zone of growth inhibition [36]. Here, multi-drug resistance is defined if a pathogen shows resistance to at least one agent in 3 or more antimicrobial classes [37].

Yeast and Other Fungal Infections

Fungi are the second major BWI-causing microbes [38]. BWIs caused by fungi are a part of mono- or polymicrobial infections, opportunistic infections, fungemia, and rare aggressive soft tissue infections [39]. These infections are mostly misdiagnosed due to the same kind of manifestations of bacterial infections and due to the lack of a suitable mycology laboratory [38]. These fungal infections have a very high mortality rate, and infection is only nonfatal when there is early diagnosis

and treatment [40,41].

From around the globe, 6.3 to 44% of all incident fungal infections have been documented from different burn centers [40,42-44]. From a case study of 220 burn patients, 42% of the BWI pathogens were reported to be *Candida* spp. [40,42-44]. Invasive *Candida* infections are one of the major causes of morbidity and mortality among burn patients [42]. Due to the introduction of new antifungals, changes in the epidemiology and drug responses of such fungal infections have been observed [45-48]. It has been found that non-albicans *Candida* is becoming increasingly resistant to the common anti-mycotic substances [45-49].

Burn patients are usually exposed to these fungal infections after the second week of their thermal injury [50]. The high mortality rate is due to the presence of fungemia, multiple positive cultures, and deep-rooted invasion of healthy skin [51]. The age of the patient, total burn size, body surface area (30%–60%), full-thickness burns, long hospital stay, long-term artificial ventilation, inhalational injury, late surgical excision, artificial dermis, central venous catheters, fungal wound colonization, open dressing, antibiotics (such as imipenem, vancomycin and aminoglycosides), steroid treatment, hyperglycemic episodes, and immunosuppressive disorders all accentuate fungal infections in burn patients [39,45-48,50].

The methods of diagnosis are conventional and mostly or-

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ganism-specific for the identification of mycoses at the burn site [45]. Direct tissue biopsy is performed in some cases [45]. However due to the voracious growth of fungal culture, sometimes it becomes too late to start an appropriate anti-mycotic therapy [45]. Burn wound samples are collected at proper time intervals for laboratory diagnosis of fungal infections [52]. The burnt tissue should be excised after the 7th, 14th, 21st, and ≥28th days [51]. Tissue biopsy is done for a demonstration of fungal wound infections, and the culture of tissue-specific biopsy is interpreted semi-quantitatively using the following formula [51]:

$$\frac{CFUs \times \log reciprocal \times 2 = colony\ count}{Tissue\ weight\ (g)}$$

In cultures, the germ tube test, characteristic growth on cornmeal agar, cultural characteristics on HiCrome agar, tetrazolium reduction test, and carbon and nitrogen assimilation tests are evaluated for yeast identification [51]. Molds are identified using lactophenol cotton blue (LPCB) wet mount preparation for conidiogenesis, pattern, and arrangement [51]. Identification of non-sporulating molds is carried out using slide cultures with potato dextrose agar [51].

E-strip or broth micro-dilution using antifungals like amphotericin B, fluconazole, itraconazole, voriconazole, and caspofungin are the tests to check for the antifungal susceptibility of yeasts [52]. The antifungal susceptibility of molds is tested by an E-strip test using amphotericin B [52]. If *Candida albicans* are isolated, a lower concentration of nystatin is needed as a local treatment in contrast to its higher concentration for the other *Candida* spp. [40,50,53]. With the burn wounds persisting longer, the propensity of fungal infections increases further [49]. Therefore, the development of pharmaceutical products to recover the wound more rapidly, advancements in topical antifungal therapy, and implementations of appropriate systemic antifungal regimes as guided by antifungal susceptibility tests help to improve the treatment outcomes for severely injured burn patients susceptible to fungal infections [50].

Viral Infections
Burn patients are very susceptible to viral infections [54]. The immunosuppressed state of the patient after an injury triggers the reactivation of latent infection. This becomes the most common cause of viral infection post-injury [54]. Administration of acyclovir for a minimum of 10 days is the most commonly used antiviral therapy to treat viral infection [54].

Herpes simplex virus infections
The frequency of both herpes simplex virus (HSV)-1 and HSV-2 infections in burn patients increases with the age of the victim [54]. There can be primary, secondary, or opportunistic HSV infections due to viral reactivation following reduced immunity in burn patients [54]. It not only impairs the healing process, prolonging the recovery time, but also causes a reduction in the number of T-lymphocytes, down-regulation of Toll-like receptor-mediated nuclear factor-κB expression, and abnormal production of interleukin (IL)-2, cytokines, and antibodies [55,56].

The viral infection manifests itself as groups of vesicopustules or rashes in the burnt area [53]. Reactivation of the latent virus in immune-debilitated burn patients causes diseases like tracheobronchitis, acute respiratory distress syndrome, pneumonia, liver necrosis, focal necrotizing hepatitis, and encephalitis [57].

Fluorescence *in-situ* hybridization, polymerase chain reaction (PCR), and next generation sequencing are common methods of detecting HSV in BWIs [54]. Intranuclear eosinophilic inclusion bodies in the viral-infected cells are also looked for under a light microscope as a characteristic marker for HSV infections [54].

Cytomegalovirus infections
Burn patients can also be affected by cytomegaloviruses (CMVs), either by primary or exogenous infection or reactivation of latent infections [54]. The infection causes anomalous immune responses involving macrophage hyperactivity, enhanced cytokine production, and over-activation of T-helper cells [58,59]. A 2011 study showed that 71% of CMV infections occurred in CMV-seropositive burn patients, while only 12.5% of CMV-seronegative burn patients were affected [60]. The associated complexities include colitis, pneumonia, organ dysfunction, and encephalitis [60]. PCR, quantitative nucleic acid testing, and immunochemistry are used to detect CMV infections [54]. Histological detection involves the observation of intra-nuclear basophilic inclusion bodies with a characteristic "owl's-eye" appearance under the light microscope [54].

Varicella zoster virus infections
Varicella zoster virus (VZV) infections in burn injuries are extremely rare, but when they occur, they are accompanied by critical post-infection complications with an increased mortality rate [61]. It is quite prevalent among pediatric burn patients [62]. PCR is the most sensitive method of detecting VZV infec-

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tions, as compared to culture, serology, or immunochemistry [54]. Sometimes microscopic observation of intranuclear inclusion bodies also confirms the presence of the virus [54]. Any previous infection by the same VZV strains or VZV vaccination lowers the rate of occurrence of VZV infections [62].

Poxvirus infections

Parapoxvirus belonging to the Poxviridae family induces infections in burn patients with skin grafts, either by direct transmission or through infected fomites by indirect transmission [62]. It affects the epidermal keratinocytes of the patients [54]. Vascular endothelial growth factor is upregulated during burn injuries, which promotes angiogenesis, thus facilitating infection [54]. Cell culture isolation, PCR, enzyme-linked immunosorbent assay, and Western blotting are some common methods of detecting the virus [54]. Treatment includes cryotherapy, electrocautery, and the administration of cidofovir or imiquimod [63]. Some large Orf disease (ecthyma contagiosum or contagious pustular dermatitis) lesions might require excision and skin grafting [64].

Human immunodeficiency virus infections

A study of burn patients living with human immunodeficiency virus (HIV) infection in Malawi showed a high probability of death if sepsis or multi-organ dysfunction developed [65]. HIV-positive patients who suffer from burn injury but do not have AIDS are treated similarly to HIV-negative patients [66]. Burn injury, along with a co-existing HIV infection, causes a depletion of CD4+ T cells and defective release of cytokines [67].

Human papillomavirus infections

Human papillomavirus (HPV) replicates when the immune system becomes under-functional in burn patients [54]. These infections were first reported in 1996 when a boy aged 4 years, with a small burn on the left ring finger, was found to develop a "keloid scar" in that burn area, four weeks after the injury [68]. HPV could survive and replicate in the wound, as the basal layer of the skin remained intact [68].

IMPACT OF GEOGRAPHICAL CONDITIONS ON THE MICROBIAL PROFILE OF BWIS

Geographical conditions play a critical role in influencing the development of infection in burn patients, shaping the microbiome found in the BWIs [69,70]. In a study conducted in a hospital in Tanzania, *Acinetobacter* spp. emerged as the main

cause of HAIs in burn patients, whereas in a study done in Nigeria on burn patients, *Klebsiella* spp. was found to be the predominant pathogen [36,71]. This difference in pathogen preponderance in BWIs is due to varying geographical conditions and different control measures [36]. The survivability of burn patients differs significantly depending on ethnicity and race, as well as on the cost and utilization of health care services [69].

IMPACT OF COVID-19 ON BURN INJURIES

Many countries resorted to social isolation and lockdown for quite a long span of time for the containment of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is the causative agent of Coronavirus disease 2019 (COVID-19), the global pandemic. This caused an increase in the occurrence of domestic accidents, leading to burn injuries, although a reduction in amenities available for burn care was observed worldwide during the pandemic, especially in lower-income countries [72].

IMPACT OF BURN INJURIES ON THE IMMUNE SYSTEM

The skin is the largest anatomical barrier and defensive against the entry of pathogens, which induces a state of immunosuppression when disrupted in burn patients [73]. Host defense has two branches, namely the innate and adaptive immune responses. Of which, the latter takes a longer time to set in [73]. The innate immune response is, however, immediate, severe, and prolonged [73]. At first, there is a pro-inflammatory response where IL-1, IL-6, tumor necrosis factor-α, and interferon-γ cytokines are secreted, and later, the anti-inflammatory response maintains homeostasis by secreting IL-10 and by transforming growth factor-β [73].

Mast cells are the first immune cells to respond to BWIs. Dendritic cells, neutrophils, and monocytes migrate to the site of inflammation under the influence of chemotactic factors [74]. Neutrophils produce reactive oxygen species to destroy the pathogens in the burn wounds, which, in turn, causes damage to skin structures and elicits a strong inflammatory response defined as systemic inflammatory response syndrome (SIRS) [73,75]. SIRS is dampened in elderly patients as compared to younger patients, despite the burn size [73].

The innate immune system is often significantly altered during major burn wounds, where neutrophil and intracellular killings are disrupted, down-regulation of major histocompat-

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ibility complex-class II expression occurs, and phagocytic activities of macrophages are diminished [76-78]. These anomalies diminish the natural defenses of the body, increasing the chances of notorious pathogen attacks in burn patients [50,79].

INFECTION CONTROL IN BURN PATIENTS

There are three types of BWIs, namely cellulitis, burn wound impetigo, and invasive wound infections within unexcised eschar (necrotizing infection-fasciitis) [80]. Regular laboratory surveillance along with routine microbial wound culturing are essential for strict infection control practices and appropriate antibacterial therapy [80]. Receiving antibiotics before the infection, as well as during the hospitalization period, is a major risk factor for the acquisition of antibiotic-resistant microorganisms [81]. Thus, routine follow-up of the antibiotic-resistance pattern of burn wound flora is absolutely mandatory for successful infection control [81]. Antibiotics must be chosen only after proper monitoring of the antibiotic resistance trend in an individual burn center to restrict infection by MDR microorganisms [80]. Also, systemic antibiotic administration should be carried out for only a very short period of time in burn patients to avoid the spread of multi-drug resistance [81].

Patients with large burn wounds need to be provided with advanced burn wound care [80]. Such advances in wound care include advances in wound exudate and edema control, optimization of the wound environment with ideal skin disinfectants, advances in wound debridement systems, and enhancements in systemic care and management through new applications of medical technologies [82].

Some useful techniques used in burn wound cleansing are high-pressure irrigation, low-pressure irrigation, swabbing, showering, bathing, and washing the affected area under a running liquid [83]. Water, saline, or other antiseptic formulations are used as the cleansing liquid, as applicable [83]. Nowadays, a large number of dressings are available, which are very effective in the healing of cleansed wounds [83]. Some therapeutic applications, involving the use of collagen, hyaluronic acid, growth factor, vacuum-assisted closure, and skin grafting are used to treat burn wounds of varying severities [40]. The Versajet hydrosurgery system is very advantageous for burn wound debridement, which includes optimal preservation of viable tissue, a reduction in blood loss, and effective elimination of bacterial colonization [84].

CONCLUSIONS

At the very outset, the prevention of burn injuries should be highly prioritized, as it stands as a global public health crisis, especially in underdeveloped and developing countries. Patients with burn injuries have increased susceptibilities to a wide range of pathogens, including various MDR species of bacteria, fungi, and viruses, particularly during their hospital stay for treatment. This occurs mainly due to their impaired immune system responses, inappropriate vascular organization within the burn-injured area, and intensification of severe oxidative stress. Immunosuppression, prolonged hospitalization, and geographical factors influence the susceptibility of burn patients to MDR-bacterial and fatal viral infections. Microbial transmission and infestation in burn wounds need to be reduced to improve the survival chances of burn patients. For this, an effective infection control policy at every stratum of health care is essential. A combined effort of burn surgeons and burn care units to control the overuse of antibiotics and provide a sterile environment and efficient medical equipment for effective and critical care of the patients should effectively tackle the otherwise sinking situation in burn care across the world.

CONFLICT OF INTEREST

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

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Conceptualization: SR. Data curation: PM, SK, DM, VRC. Methodology: PM, SK, DM, VRC. Writing–original draft: PM, SK, DM, VRC, Writing–review & editing: SR, LC.

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Beyond survival: understanding post-intensive care syndrome

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Post-intensive care syndrome (PICS) refers to persistent or new onset physical, mental, and neuro-cognitive complications that can occur following a stay in the intensive care unit. PICS encompasses muscle weakness; neuropathy; cognitive deficits including memory, executive, and attention impairments; post-traumatic stress disorder; and other mood disorders. PICS can last long after hospital admission and can cause significant physical, emotional, and financial stress for patients and their families. Several modifiable risk factors, such as duration of sepsis, delirium, and mechanical ventilation, are associated with PICS. However, due to limited awareness about PICS, these factors are often overlooked. The objective of this paper is to highlight the pathophysiology, clinical features, diagnostic methods, and available preventive and treatment options for PICS.

Key Words: ABCDEF bundle; cognitive impairment; COVID-19; impaired muscle regeneration; intensive care unit; postintensive care syndrome

INTRODUCTION

Intensive care and emergency medicine have undergone significant advancements in the last few decades, which have led to a dramatic improvement in the short-term prognosis and survival rates of intensive care unit (ICU) patients. However, a similar effect has not been observed in quality of life or long-term outcomes [1], and the incidence of new onset or worsening of physical, mental, and neurocognitive health complications in patients following a period of stay in the ICU, collectively referred to as post-intensive care syndrome (PICS), has increased [2]. Physical impairments associated with PICS are largely due to ICU-acquired muscle weakness (ICU-AW), which includes multiple disorders including critical illness neuromyopathy and muscle deconditioning and commonly presents as skeletal muscle weakness and difficulty weaning from the ventilator [3]. Neurocognitive impairments span multiple domains including visuospatial skills, visual and working memory, attention,

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and executive function [4]. Psychiatric impairments include post-traumatic stress disorder (PTSD), anxiety disorders, and depressive disorders [5]. The effects of PICS can last long after hospital admission, causing patients and their families physical, emotional, and financial stress. Psychiatric and neurocognitive impairments may also be experienced by family members of the patients, which is referred to as PICS-F [6]. A multicenter prospective cohort study from the United States found one or more PICS problems in as many 60% of survivors of a critical illness following ICU admission and co-occurring PICS problems in 20% of survivors of a critical illness following ICU admission [7].

PICS affects one of every five adult patients within 1 year after discharge from a critical care facility [8]. Several modifiable risk factors such as duration of sepsis, delirium, and mechanical ventilation are associated with PICS; controlling these risk factors is associated with lower rates of PICS [7]. A higher incidence of physical and neurocognitive impairments has been reported in patients who underwent a prolonged period of hypoxemia and acute respiratory distress syndrome [9]. Factors such as female sex, pre-existing psychological disorders, inflammation, communication barriers, administration of analgesics, and a negative ICU experience may contribute to the psychiatric aspects of PICS [8]. Higher rates of PTSD were recorded in patients undergoing unplanned admission and surgery, presumably because these patients had less time to prepare psychologically than those who underwent elective surgery. Most studies regarding PICS have been conducted in Europe and the United States, with little data from Asian countries. Recent studies from South and East Asian countries have reported a low incidence of PTSD [10]. However, PICS was documented in multiple countries in Europe as well as China and the United States during the coronavirus disease 2019 (COVID-19) pandemic; symptoms of dyspnea, fatigue, and psychological distress were reported after discharge by ICU patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [11]. In addition, Halpin et al. [12] reported a high incidence of breathlessness in Black, Asian, and minority ethnic groups at 4–8 weeks after discharge.

Prevention of PICS requires a multidisciplinary approach involving nurses, social workers, and psychologists. Adequate emotional support requires good communication between the discharged patient and the healthcare team, family support in the ICU, and psychological and behavioral therapies. Early nutrition therapy along with early mobilization play crucial roles in preventing physical impairment, including ICUAW

KEY MESSAGES

- Post-intensive care syndrome refers to the persistent or newly onset physical, mental, and neurocognitive complications that can occur following a stay in the intensive care unit.
- It was extensively observed during coronavirus disease 2019 (COVID-19) pandemic in the United States among other countries.
- Its manifestations include physical impairments, including impaired muscle regeneration, cognitive impairment, and psychological impairment.

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[13]. While no association between socioeconomic and PICS-free status has been reported, studies have demonstrated an association between higher number of years of education and higher odds of being PICS-free. This could be due to unmeasured factors such as health literacy, access to health care, and better health behaviors. In addition, frailty is associated with higher rates of mortality and morbidity, with higher Clinical Frailty Scale scores associated with a lower odds of being PICS-free [7]. The purpose of this article is to provide a comprehensive review of PICS including its pathophysiology, prevention strategies, and treatment modalities to increase awareness among medical students, residents, and healthcare professionals.

PATHOPHYSIOLOGY

A dramatic improvement in ICU survival rates have inadvertently resulted in a significantly larger burden of patients who suffer from post-ICU sequelae; however, there is a lack of familiarity and understanding of these post-ICU sequelae (Figure 1).

PHYSICAL IMPAIRMENTS

ICU-AW is the most common and debilitating physical manifestation of PICS and is characterized by symmetrical weakness of the body. This can be subcategorized as critical illness myopathy, which affects the muscles; critical illness polyneuropathy, which affects the nerves; or critical illness neuromyopathy, in which both nerves and muscles are affected. Diagnosis is based on a combined score less than 48 on the Medical Research Council scale after grading all testable muscle groups

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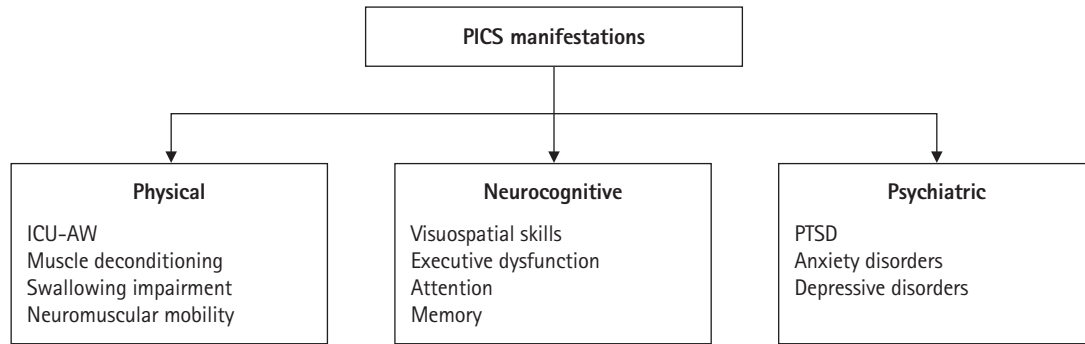
Figure 1. Post-intensive care syndrome (PICS) manifestations. ICU-AW: intensive care unit–acquired muscle weakness; PTSD: post-traumatic stress disorder.

based on values recorded 24 hours apart [14]. Other contributing factors to weakness include joint contractures due to limited mobility and ectopic ossifications [4]. The pathogenesis of ICU-AW involves multiple factors that can act independently or in combination. The sequence of events is described below.

Muscle Degradation Due to Proteolysis during the Phase of Acute Insult

Microvascular dysfunction plays a pivotal role in the acute phase of critical illnesses and is heavily implicated in the pathogenesis of ICU-AW. Microvascular dysfunction ensues in conditions involving systemic inflammation such as sepsis and results in the transformation of endothelial cells to a pro-inflammatory phenotype. This involves shedding of the endothelial glycocalyx, alterations in the endothelial barrier function, and a subsequent increase in vascular permeability. Proinflammatory transformation of endothelial cells is a key feature of critical illnesses and involves upregulated expression of the inflammatory cytokines tumor necrosis factor (TNF)-α, interleukin (IL)-1, and IL-6, which are all involved in muscle degradation [15]. TNF-α propagates catabolic pathways by promoting increased expression of genes associated with the ubiquitin-proteasome system responsible for massive intracellular proteolysis. IL-1, which is often found in the blood of patients with critical illnesses, has also been identified as a contributor to skeletal muscle atrophy by inhibiting protein synthesis, while IL-6 is involved in both the regulation of protein synthesis and protein degradation [16,17].

Impaired Muscle Regeneration during the Recovery Phase

In those with ICU-AW, impaired muscle degeneration is attributed to the loss of satellite cells, also known as myogenic stem cells, which are located beneath the basal lamina of mus-

cle fibers and proliferate to give rise to myoblasts [18]. Depletion of satellite cells is associated with depletion of endothelial cells as they share regulatory factors such as vascular endothelial growth factor, and notch signaling from endothelial cells drives satellite cells into quiescence, which can potentially lead to satellite cell depletion [19]. Other instrumental mechanisms in ICU-AW include dysregulation of autophagy, which is essential for degradation of damaged cellular components and maintenance of cell homeostasis. Dysregulation of autophagy is associated with muscle wasting and occurs in critical illnesses as a result of the large number of damaged cellular components that accumulate due to inflammation. Mitochondrial dysfunction is also common in ICU-AW, rendering skeletal muscle cells unable to meet their cellular energy demands (Figure 2).

COGNITIVE IMPAIRMENTS

Various mechanisms are involved in the development of long-term cognitive impairment in PICS. One such mechanism is neuronal apoptosis triggered by dopamine receptor activation in response to vagal signals. The vagus nerve is responsible for carrying afferent signals from the peripheral organs to the brain stem, where multi-synaptic pathways are activated. This nerve responds to stimuli such as the stretch reflex in the lungs (particularly in the case of mechanical ventilation) or inflammation (via toll-like receptor-4, IL1R or TNF). Additionally, the vagus nerve is dependent on dopaminergic signaling, which potentiates hippocampal apoptosis [20]. Alongside the aforementioned factors, systemic endothelial dysfunction has also been proposed to play a key role in the development of acute brain injury in ICU survivors. Endothelial dysfunction is a central feature of inflammatory states such as sepsis, and the

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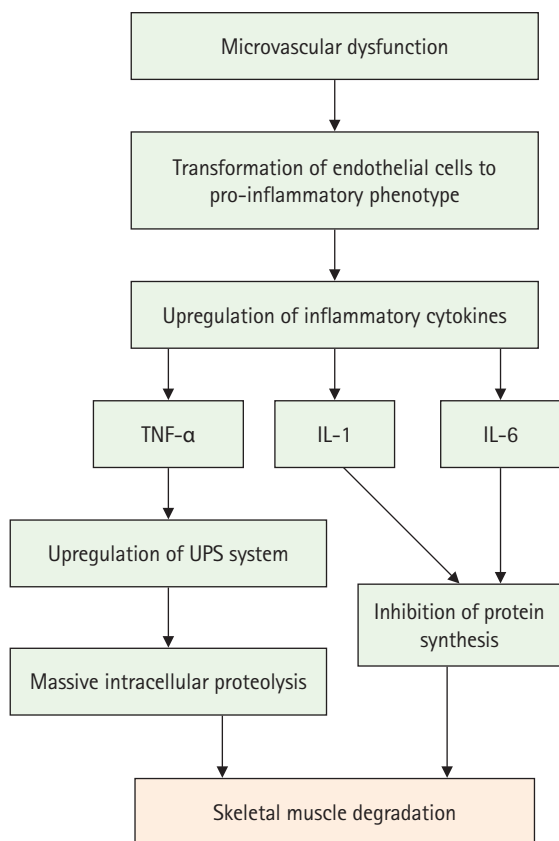
Figure 2. Muscle pathophysiology. TNF: tumor necrosis factor; IL: interleukin; UPS: ubiquitin–proteasome system.

Figure 3. Cognitive pathophysiology. IL: interleukin.

blood-brain barrier, which comprises endothelial cells, could be vulnerable to the same dysfunction. Endothelial activation can result in increased expression of adhesion molecules and coagulation mediators that can increase blood-brain-barrier permeability, alongside which cerebral hypoperfusion and thrombosis make the brain vulnerable to insult [21]. Cerebral hypoperfusion and thrombosis have been implicated in the development of cerebral ischemia, which can induce white matter changes that may eventually manifest as long-term cognitive impairments (Figure 3) [22].

PSYCHOLOGICAL IMPAIRMENTS

Anxiety, depression, and PTSD, all of which are stress-related, are the most common psychological manifestations of PICS, and patients typically present with a combination of these conditions. A negative ICU experience and delirium are significantly associated with development of psychological impairments in post-ICU patients [6]. Delirium in ICU patients is

thought to be caused by various mechanisms including loss of central cholinergic activity, increased dopaminergic activity, central nervous system inflammation, hypoxemia, cerebral hypoperfusion, hyponatremia or hypernatremia, and hypoglycemia. Other associated factors include increased glucocorticoid levels during stress and disturbance of the circadian rhythm [23]. In addition to delirium, prolonged sedation, use of benzodiazepines and vasopressors, and lack of social support during the illness are all thought to contribute to psychological impairments in post-ICU patients [24]. Correlations between psychiatric symptoms and post-ICU sleep disturbances have been reported in previous studies [25]. Post-ICU trauma symptoms and depression symptoms are associated with post-ICU sleep disturbances including insomnia, hypersomnia, and excessive day-time sleepiness (Figure 1) [25].

DISCUSSION

Increased use of ICU services and advancements in the diagnosis and treatment of life-threatening conditions such as multiple organ system failure, respiratory failure, sepsis, and shock has resulted in growing numbers of ICU survivors [26]. PICS refers to a complex of symptoms experienced by ICU survivors and characterized by persistent or new onset impairments in physical, cognitive, and psychological components that can negatively affect the quality of life of both the patient and their family.

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Approximately 50%–70% of all ICU survivors have at least one PICS-related disability, and these disabilities may persevere for 5–15 years following discharge. Among ICU survivors, nearly 50% have PICS-related physical impairments, and 30%–80% have PICS-related cognitive deficits. These impairments are more prevalent in older individuals [27]. PICS has mostly been evaluated in the primary care setting in the United States. Although identification of PICS symptoms can be difficult, certain aspects of the ICU recovery center, which is a model initiated by Vanderbilt University in 2012, may help diagnose PICS symptoms. In this model, initial evaluation occurs 2 weeks post-hospital discharge and includes spirometry and a 6-minute walk test to evaluate physical impairment. In addition, medication reconciliation and counseling are performed, and the ICU course and related active medical problems are reviewed. Targeted case management assessment; screening for depression, anxiety, and PTSD; and cognitive assessment using the Montreal Cognitive Assessment or Mini-Mental Status exam are also recommended [3,28]. Because executive function is the most commonly affected cognitive domain in PICS, the Society of Critical Care Medicine recommends employing the Montreal Cognitive Assessment, which incorporates an executive function component and is a sensitive detector of mild cognitive impairment [29]. The physical function intensive care test, which has excellent reliability and sensitivity, can also be used to monitor changes in strength and functional outcomes in the ICU. In mechanically ventilated tracheostomy patients who are able to stand, this test can measure endurance, strength, cardiovascular capacity, and functional level and can be repeated after weaning from ventilation [30]. Several prognostic factors such as pre-existing disability, frailty, or nursing home use can be used to predict a patient's likelihood of complete recovery from intensive care. Patients who have pre-existing disabilities, are frail, and/or who reside in a nursing home are less likely to regain functional independence than previously healthy patients. The National Institute for Health and Care Excellence's Guidelines on Rehabilitation after Critical Illness recommend multi-professional rehabilitation after critical illness, starting in the ICU and continuing in the ward and after hospital discharge [31]. Guidelines from the Society of Critical Care Medicine's updated Surviving Sepsis Campaign 2021 recommend screening for financial and social support for patients and families and shared decision-making in discharge planning and medications, mentioning sepsis and common impairment after sepsis in the discharge summary, and evaluating for physical, mental, and emotional issues after

hospital discharge. Other recommendations include using a critical care transitional program for ICU-to-floor transitions; a hand-off procedure for care transitions; verbal and written sepsis education; and referral of patients to peer support groups, post-critical illness follow-up programs, and outpatient rehabilitation centers [32].

The risk of PICS can be reduced by avoiding sedation, psychotropic use, hypoglycemia, hypoxemia, and environmental modifications and by ensuring early physical rehabilitation and mobility for older people [30]. The Pain, Agitation, and Delirium guidelines are being implemented in ICU care at more than 70 major hospitals across the United States through the ICU Liberation Collaborative, a real-world quality improvement initiative. These guidelines employ the ABCDEF bundle, an evidence-based strategy, to prevent PICS [33]. "A" stands for "assessment, prevention, and management of pain," while "B" represents both spontaneous awakening trials and spontaneous breathing trials, as well as coordination of these trials between nurses and respiratory therapists. "C" represents choice of sedation and analgesia. Numerous studies have shown that patients who are kept "awake and alert" or barely sedated with drugs other than GABAergic benzodiazepines spend less time on a ventilator and are more likely to be delirium-free. "D" stands for delirium assessment, prevention, and management and allows identification of otherwise overlooked delirium and triggers patient-centered interventions to shorten the length of brain dysfunction through adherence to each of the bundle pieces. "E" stands for early mobility and exercise. This part of the bundle necessitates an aggressive approach by the team (not just the therapists, but also the nurses). This can be extremely difficult at times because it requires taking intubated patients off sedation and getting them out of bed. "F" stands for family engagement and empowerment (Table 1) [34].

Compliance is a crucial aspect of prevention and management of PICS since changes in compliance with different ele-

Table 1. Preventing PICS, the ABCDEF bundle

ABCDEF bundle
A: Assess and manage pain
B: Both spontaneous awakening trials and spontaneous breathing trials
C: Choice of sedation and analgesia
D: Delirium assessment and management
E: Early mobility and exercise
F: Family engagement and empowerment

PICS: post-intensive care syndrome.

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Table 2. Pharmacological intervention of post-intensive care syndrome

Study	Drug	Use	Mechanism
Bryant et al. [36]	Magnesium sulphate	Neuroprotective	Blockage of N-methyl-D-aspartate channels and voltage-gated calcium channels
McIntosh et al. [37]	Disodium 2,4-disulfophenyl-N-tert-butylnitrone (NXY-059)	Antioxidant effects and vascular protective properties	Free radical scavenger
Shuaib et al. [38]	Melatonin	Neuroprotective agent and maintenance of circadian rhythm	Alteration of catalase, glutathione peroxidase, and superoxide dismutase; and attenuation of the activation of nuclear factor-kappa B and activator protein 1
Shuaib et al. [38]	Curcumin	Anti-inflammatory, anti-oxidant, analgesic, and hepatoprotective properties	Reduction in the expression of matrix metalloproteinases, attenuation of interleukin-1, and inhibition of p38 mitogen-activated protein kinases/protein kinase C pathways
Panahi et al. [39] Hurtado et al. [40]	Citicoline	Neuroprotective	Increase activity of glutathione reductase, lipid peroxidation attenuation, increase of sirtuin 1 expression

Table 3. Differential diagnosis of post-intensive care syndrome

Differential diagnosis
1. Stroke
2. Endocrine abnormalities
3. Alzheimer disease
4. Severe depression
5. Spine disorders
6. Post–COVID-19 syndrome
7. Myopathies
8. Neuropathies
9. Nutritional deficiencies
10. Electrolyte abnormalities

COVID-19: coronavirus disease 2019.

ments of the ABCDEF bundle and other treatment strategies can alter and even negate outcome benefits. Various studies have shown that patients do not improve if compliance is not high and if all the elements of the ABCDEF bundle are not followed [33]. Due to the strong connection between nutritional therapy and PICS, nutritional therapy is crucial for PICS prevention. Appropriate energy delivery and protein intake are the most essential components of muscle synthesis; however, overfeeding should be avoided as it could induce autophagy and worsen PICS [1]. Another method to prevent PICS is an ICU diary, a record of medication and interventions kept for ICU patients while they are sedated and ventilated. It is written by family members, nurses, and others. After discharge, the patient can read the diary and gain a better understanding of what has occurred. This has been shown to reduce PTSD symptoms in patients and their families [35].

Given that oversedation contributes to the development of cognitive and psychiatric symptoms, guidelines recommend decreased use of sedation for ventilated patients. Customized sedation and analgesia management for individual patients is crucial to avoid cognitive impairment, such as confusion and delirium; these interventions also reduce pain and improve mobility. Environmental changes are useful in lowering the likelihood of delirium. Dark rooms, constant noise, and frequent interruptions have all been associated with disturbance of the sleep-wake cycle, which may induce delirium and should be avoided. Anticholinergics, opioids, and sedative medicines should be used cautiously in the treatment of delirium [36].

Follow-up of patients discharged from the ICU can be performed at intensive care follow-up clinics, which can also be used as locations to diagnose and treat PICS. Although mainly used in Europe, these follow-up clinics are gradually being introduced in North America. There is no fixed template for these types of facilities or patient evaluation methods, and treatment modalities may vary. Reduction of PTSD symptoms among follow-up patients at these clinics may be due to individualized interventions; more research is required to establish the usefulness of these facilities (Tables 2 and 3) [1].

CONCLUSIONS

A plethora of impairments spanning physical, psychiatric and neurocognitive domains is increasingly being seen in patients following a period of stay in intensive care facilities; these impairments have an adverse long term impact on the well-being of both patients and their families. Several modifiable and non-modifiable factors spanning patient demographics such as age, sex, race, preexisting disabilities, frailty, hypoxia, and negative ICU experiences have been reported to increase the

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risk of PICS. Catabolic pathways leading to muscle degeneration and neuronal apoptosis along with endothelial dysfunction can lead to various impairments. A multimodal approach addressing contributing factors, communication techniques, and involvement of psychotherapy as well as physical and nutritional therapy needs to be incorporated into ICU care to decrease the incidence of PICS. Assessment of physical and neurocognitive function along with screening for psychiatric disorders at regular follow-up visits is important to identify and manage PICS early in its disease course. Future studies are required to gain a better understanding of the pathophysiology of PICS and to identify prevention and treatment strategies.

CONFLICT OF INTEREST

FUNDING

ACKNOWLEDGMENTS

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Comparative evaluation of tocilizumab and itolizumab for treatment of severe COVID-19 in India: a retrospective cohort study

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Background: Itolizumab downregulates the synthesis of proinflammatory cytokines and adhesion molecules by inhibiting CD6 leading to lower levels of interferon-γ, interleukin-6, and tumor necrotic factor-α and reduced T-cell infiltration at inflammatory sites. This study aims to compare the effects of tocilizumab and itolizumab in the management of severe coronavirus disease 2019 (COVID-19).

Methods: The study population was adults (>18 years) with severe COVID-19 pneumonia admitted to the intensive care unit receiving either tocilizumab or itolizumab during their stay. The primary outcome was clinical improvement (CI), defined as a two-point reduction on a seven-point ordinal scale in the status of the patient from initiating the drug or live discharge. The secondary outcomes were time until CI, improvement in PO_2/FiO_2 ratio, best PO_2/FiO_2 ratio, need for mechanical ventilation after administration of study drugs, time to discharge, and survival days.

Results: Of the 126 patients included in the study, 92 received tocilizumab and 34 received itolizumab. CI was seen in 46.7% and 61.7% of the patients in the tocilizumab and itolizumab groups, respectively and was not statistically significant (P=0.134). The PO_2/FiO_2 ratio was significantly better with itolizumab compared to tocilizumab (median [interquartile range]: 315 [200–380] vs. 250 [150–350], P=0.043). The incidence of serious adverse events due to the study drugs was significantly higher with itolizumab compared to tocilizumab (14.7% vs. 3.3%, P=0.032).

Conclusions: The CI with itolizumab is similar to tocilizumab. Better oxygenation can be achieved with itolizumab and it can be a substitute for tocilizumab in managing severe COVID-19.

Key Words: COVID-19; itolizumab; management; tocilizumab

Original Article

INTRODUCTION

The coronavirus disease 2019 (COVID-19) continues to impact millions of people worldwide, prompting the science community to explore new strategies for its management. In severe COVID-19, there is a marked increase in the levels of cytokines (e.g., interleukin [IL]-6, IL-1, and IL-18 and tumor necrotic factor [TNF]) and chemokines, often referred to as a "cytokine

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storm" [1]. Other inflammatory markers like C-reactive protein (CRP), D-dimer, lactate dehydrogenase (LDH), and ferritin are also elevated. Hence, anti-inflammatory drugs, such as IL-6 inhibitors, IL-1 receptor antagonists, and TNF-α inhibitors have emerged as potential therapeutic agents to attenuate the release of inflammatory mediators [2].

Tocilizumab is a humanized monoclonal inhibitor of the proinflammatory cytokine IL-6 and is licensed for use in the clinical management of cytokine release syndrome in COVID-19 [3]. Two large trials have shown that the use of tocilizumab has mortality benefits in severe COVID-19 [4,5].

Itolizumab is an anti-CD6 monoclonal antibody initially developed for various cancers but is now being repurposed for COVID-19 [6]. Itolizumab, by inhibiting CD6, downregulates the synthesis of proinflammatory cytokines and adhesion molecules, eventually leading to reduced interferon-γ, IL-6, and TNF-α and reduced T-cell infiltration at inflammatory sites [7]. Itolizumab has multiple sites of action and is expected to be better than tocilizumab in the management of COVID-19. Some studies have shown promising results with itolizumab [8,9], but no randomized controlled trial has confirmed its effectiveness. Although itolizumab has a similar mechanism of action to tocilizumab, no available study compares the two drugs in the management of COVID-19.

MATERIALS AND METHODS

Study Design and Participants
This retrospective, observational cohort study was conducted in a tertiary care hospital in India on patients with severe COVID-19 pneumonia. The study population was adults (>18 years) with severe COVID-19 pneumonia confirmed on real-time reverse transcriptase polymerase chain reaction of nasopharyngeal swabs and who had been admitted to the intensive care unit (ICU) of the center between March 2021 and June 2021.

Inclusion criteria were patients with severe COVID-19 pneumonia, defined as the clinical signs of pneumonia (fever, cough, dyspnea) plus one of the following: respiratory rate >30 breaths/min; severe respiratory distress or oxygen saturation (SpO_2) <90% on room air; or PO_2/FiO_2 <300 at the time of admission and were treated with either tocilizumab or itolizumab during the course of their stay in the ICU. Exclusion criteria were pregnancy, death within 72 hours of therapy after excluding the adverse effects of the drugs, and patients with insufficient medical information. The exclusion criteria for using

> **KEY MESSAGES**
> - Itolizumab, an interleukin-6 inhibitor, has multiple sites of action and is expected to be better in the management of coronavirus disease 2019 (COVID-19) than tocilizumab.
> - The clinical improvement and survival rates with itolizumab are similar to those of tocilizumab; however, tocilizumab has a better safety profile compared to itolizumab.
> - Better oxygenation can be achieved with itolizumab and it can be a substitute for tocilizumab in managing severe COVID-19.

tocilizumab and itolizumab were based on the manufacturer's recommendations.

The study was approved by the Institutional Ethics Committee of All India Institute of Medical Sciences Patna, India (Ref no. AIIMS/Pat/IEC/2021/780). The need for informed consent was waived.

Data Extraction
Patients treated with tocilizumab or itolizumab were identified retrospectively by ICU records. A subsequent review of the medical records of each patient was performed to collect demographic, clinical, and laboratory information.

The following clinical information was recorded: (1) history of coexisting diseases; (2) receipt of corticosteroid, plasma therapy, or remdesivir; (3) type and duration of respiratory support; (4) PO_2/FiO_2 ratio; (5) adverse effects due to drugs; and (6) outcome. The following laboratory data were collected: total leukocyte count (TLC), D-dimer, ferritin, IL-6, LDH, CRP, and procalcitonin. Survival days were calculated from the day that tocilizumab/itolizumab was started to either death or discharge from the hospital. The study aimed to assess the effects of tocilizumab and itolizumab in managing severe COVID-19. The primary outcome of the study was clinical improvement (CI), defined as an at least two-point reduction on a seven-point ordinal scale in the status of patients from the time of initiating the drug or live discharge from the hospital, whichever came first.

The seven-point scale was defined as follows: 7, death; 6, hospitalisation with invasive mechanical ventilation (MV); 5, hospitalisation with non-invasive ventilation/high-flow nasal cannula; 4, hospitalisation with oxygen therapy through a non-rebreathing mask (FiO_2 requirement >50%); 3, hospital-

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isation with oxygen therapy on low flow (FiO$_2$ requirement 24%–50%); 2, hospitalisation not requiring oxygen therapy; 1, discharged or achieved discharge criteria (defined as clinical recovery i.e., normalization of pyrexia, respiratory rate 12–24 breaths per minute, a saturation of peripheral oxygen >94% on room air, and relief of cough, all maintained for at least 72 hours).

The secondary outcomes were (1) time until CI, (2) improvement in PO$_2$/FiO$_2$ ratio (defined as an increase of more than 100), (3) time to improvement in PO$_2$/FiO$_2$ ratio, (4) maximum PO$_2$/FiO$_2$ ratio, (5) need for MV after administration of study drugs, (6) duration of requirement for supplemental oxygen/non-invasive ventilation/invasive ventilation, (7) time to discharge (day of drug administration to discharge from the hospital), (8) survival days, (9) frequency of serious adverse events, and (10) mortality.

Management

All patients admitted to the ICU received standard care treatment according to the COVID-19 clinical management guidelines released by the Director-General of Health Services, Ministry of Health and Family Welfare, New Delhi, India [10]. Standard of care treatment at our institute included oxygen therapy depending on the clinical condition of the patient with a target SpO$_2$ of 92%–96%, dexamethasone (6 mg for 10 days), and low-molecular-weight heparin for deep vein thrombosis prophylaxis. Remdesivir (200 mg IV on day 1 followed by 100 mg IV daily for 5 days) and plasma therapy were administered at the discretion of the treating clinician, according to the management guidelines [10].

In addition to standard care, IL-6 inhibitors like tocilizumab or itolizumab were given to patients with severe COVID-19 if they met the criteria for cytokine storm syndrome [11]. Tocilizumab (Actemra; Cipla Ltd.) was given at a dose of 8 mg/kg and repeated after 12–24 hours. Itolizumab (Alzumab/Alzumab-L, Biocon Biologics) was given at a dose of 1.6 mg/kg. A second dose of 0.8 mg/kg was given after 1 week if required.

Statistical Analysis

Categorical data were expressed as frequency and percentage. Continuous data were reported as the mean with standard deviation or median and interquartile range. The normality of the data was checked using the Shapiro-Wilk test and Q-Q plot. Parametric quantitative data were compared using an unpaired t-test. Non-parametric continuous variables were compared using the Mann-Whitney U-test. Categorical data were

compared with the chi-square test or Fisher's exact test. Multivariate logistic regression analysis was performed to assess the effects of multiple variables on the outcome. Kaplan-Meier method and log-rank P-value were used to compare the survival days and days to CI in the ICU. A P-value <0.05 was treated as statistically significant. Statistical analysis was conducted using SPSS software version 26 (IBM Corp.).

RESULTS

During the study period, 134 patients who were admitted to the ICU with COVID-19 received either tocilizumab or itolizumab. Of these, eight patients did not satisfy the exclusion criteria. Consequently, 127 patients were included in the study; 92 received tocilizumab and 34 received itolizumab. Most patients received two doses of tocilizumab and a single dose of itolizumab (Figure 1).

Eighty-one patients were on MV (invasive or non-invasive) at the time of administration of the study drugs, and 45 patients were on oxygen therapy. Of the 81 patients, 37 had severe acute respiratory distress syndrome (ARDS), 41 had moderate ARDS, and three had mild ARDS. which was defined as by Berlin [12].

Of the patients in our study, 76% were male and the median age was 62 years. At the time of drug administration, the median PO$_2$/FiO$_2$ ratio was 110 and 33.3% of the patients had severe ARDS. There was no significant difference between age, sex, comorbidities, baseline PO$_2$/FiO$_2$, and MV at the time of

Figure 1. Study cohort.

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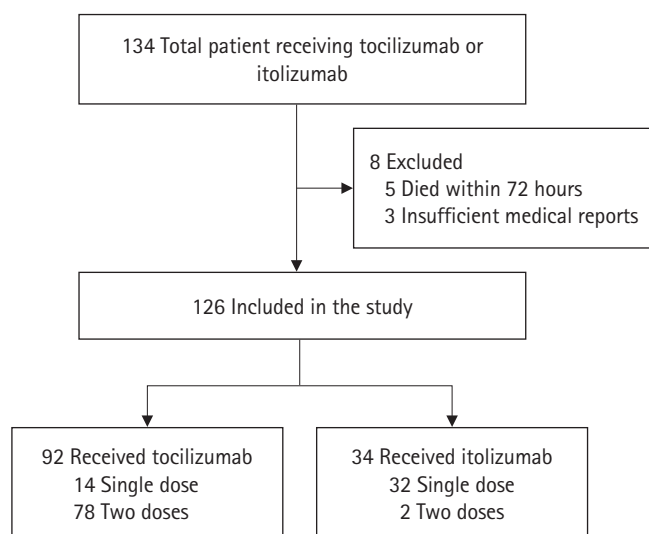
Table 1. Comparison of demographics and baseline characteristics of the patients

Baseline characteristics	Tocilizumab (n= 92)	Itolizumab (n= 34)	P-value
Age (yr)	62 (53–70)	62 (50–64)	0.466
Sex (male:female)	70:22	26:8	0.170
Any comorbidity	73 (79)	26 (76)	0.727
Diabetes	48 (52)	19 (56)	0.711
Hypertension	48 (52)	17 (50)	0.828
Chronic renal insufficiency	4 (4)	2 (3)	0.661
Hypothyroidism	9 (10)	2 (3)	0.726
Cardiovascular disease	4 (4)	3 (9)	0.386
MV at study drug administration (invasive or non-invasive)	62 (67)	19 (56)	0.171
Baseline PO_2/FiO_2 ratio at study drug administration	100 (81–150)	120 (100–152)	0.268
Time to infusion of study drug after admission (day)	5 (3–7)	4 (3–6)	0.312
Use of corticosteroids	83 (90)	30 (88)	0.745
Use of remdesivir	86 (93)	32 (94)	0.896
Use of plasma therapy	67 (73)	26 (76)	0.680
TLC (1,000/μl)	12 (9–14.9)	14 (10.8–17.2)	0.121
D-dimer (μg/ml)	1.15 (0.72–2.55)	1.01 (0.7–1.91)	0.594
Ferritin (ng/ml)	735 (379–958)	411 (331–979)	0.466
IL-6 (pg/ml)	55 (23–175)	82 (44–219)	0.066
LDH (U/L)	1,076 (856–1,349)	1,100 (760–1,329)	0.781
CRP (mg/l)	98 (56–153)	106 (51.5–127.5)	0.644
Procalcitonin (ng/ml)	0.82 (0.60–1.30)	0.80 (0.45–1.20)	0.335

Values are presented as median (interquartile range) and number (%).
MV: mechanical ventilation; PO_2: partial pressure of oxygen; FiO_2: fraction of inspiratory oxygen concentration; TLC: total leukocyte count; IL: interleukin; LDH: lactate dehydrogenase; CRP: C-reactive protein.

administration of drugs in the two groups (Table 1). The use of dexamethasone, remdesivir, and plasma therapy was also comparable in the two groups (Table 1).

CI was seen in 46.7% and 61.7% of the patients in the tocilizumab and itolizumab groups, respectively, differences there were not significant (P=0.134). The time to CI was also non-significantly different between the tocilizumab and itolizumab groups (median [interquartile range]: 12 days [9–16] vs. 11 days [7–12.5], P=0.253) (Table 2). In our study, all-cause mortality at 28 days was significantly lower in those receiving itolizumab compared to the tocilizumab group (32.3 vs. 54.3%, P=0.028). All-cause mortality at 60 days was lower with itolizumab compared to tocilizumab (38.2% vs. 56.5%), but the difference was not significant (P=0.068).

The patients were stratified based on IL-6 levels. A total of 86 patients with baseline IL-6 levels >30 pg/ml was placed into the high-level group. The CI in patients with higher IL-6 levels was significantly higher with itolizumab compared to tocilizumab (67% vs. 43%, P=0.035). Mortality at 28 days in patients with a higher level of IL-6 was also significantly lower with

itolizumab compared to tocilizumab (27% vs. 55%, P=0.011) (Table 3).

The improvement in the PO_2/FiO_2 ratio after treatment was not significant between groups. However, the number of days required to achieve an improvement of 100 units in the PO_2/FiO_2 ratio was significantly less with itolizumab compared to tocilizumab (6 days [4–8] vs. 8 days [6–12], P=0.028). The best PO_2/FiO_2 ratio achieved was also significantly better with itolizumab compared to tocilizumab (315 [200–380] vs. 250 [150–350], P=0.043). The numbers of patients needing MV and weaned from it after administration of study drugs were comparable between the groups.

Duration of patients on MV, oxygen therapy, and time to discharge were also comparable in the two groups (Table 2). The incidence of serious adverse events due to the study drugs was significantly higher with itolizumab compared to tocilizumab (14.7% vs. 3.26%, P=0.032). In the tocilizumab group, two patients had a high-grade fever and one had liver dysfunction after therapy. In the itolizumab group, two patients had bronchospasm, two patients had a high-grade fever, and one

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Table 2. Comparison of the outcome variables in tocilizumab and itolizumab groups

Variable	Tocilizumab (n=92)	Itolizumab (n=34)	P-value
Clinical improvement	43 (46.7)	21 (61.7)	0.134
Day of clinical improvement	12 (9–16)	11 (7–13)	0.253
Mortality (28 days)	50 (54.3)	11 (32.3)	0.028
Mortality (60 days)	52 (56.5)	13 (38.2)	0.068
PO_2/FiO_2 ratio improvement	50 (54.3)	23 (67.7)	0.180
Day of PO_2/FiO_2 ratio improvement	8 (6–12)	6 (4–8)	0.028
Maximum PO_2/FiO_2 ratio	250 (150–350)	315 (200–380)	0.043
Need for MV after therapy	12 (13.0)	4 (11.7)	0.848
Weaned from MV after therapy	16 (17.4)	6 (17.6)	0.973
Patients on MV during the stay	73 (79.3)	23 (67.6)	0.171
MV days	10 (5–13)	8 (7–10)	0.821
Oxygen therapy days	11 (4–16)	10 (5–14)	0.787
Time to discharge	20 (16–26)	20 (15–23)	0.375
Serious adverse event	3 (3.3)[a]	5 (14.7)[b]	0.032
AKI	5 (5.4)	2 (5.9)	1.000
Sepsis	12 (13.0)	4 (12.5)	1.000

Values are presented as number (%) or median (interquartile range).
PO_2: partial pressure of oxygen; FiO_2: fraction of inspiratory oxygen concentration; MV: mechanical ventilation; AKI: acute kidney injury.
a) High-grade fever: 2, liver dysfunction: 1, bronchospasm: 2; b) High-grade fever: 2, arrhythmia: 1.

Table 3. Clinical Improvement and 28-day mortality in patients with high IL-6 (>30 pg/ml)

Variable	Tocilizumab (n=56)	Itolizumab (n=30)	P-value
Clinical improvement	24 (43)	20 (67)	0.035
28-Day mortality	31 (55)	8 (27)	0.011

Values are presented as number (%).
IL: interleukin.

had arrhythmias. There were no deaths due to adverse events in either of the groups. Extrapulmonary complications, such as acute kidney injury and sepsis, were comparable in the two groups (Table 2).

Multivariate logistic regression was carried out to assess the effects of factors on the likelihood of CI. The following factors were considered in the multivariate analysis: age; sex; comorbidities of hypertension, diabetes, chronic kidney disease, coronary artery disease, or hypothyroidism; MV at baseline; study drugs; treatment with remdesivir; plasma therapy; PO_2/FiO_2 ratio at baseline; and baseline laboratory results of like TLC, ferritin, LDH, CRP, D-dimer, IL-6, and procalcitonin. The overall model was significant compared to the null model (χ^2

Table 4. Multivariate logistic regression analysis of factors affecting clinical improvement

Variable	OR (95% CI)	P-value
Age (yr)	1.12 (1.00–1.26)	0.343
Sex		0.893
Male	0.86 (0.21–3.48)	
Female	Reference	
Comorbidity		0.009
Present	Reference	
Absent	24.66 (2.19–277.06)	
Hypertension		0.514
Present	Reference	
Absent	1.61 (0.38–6.81)	
Diabetes		0.110
Present	Reference	
Absent	3.5 (0.21–4.66)	
CKD		0.618
Present	Reference	
Absent	2.12 (0.04–18.93)	
CAD		0.122
Present	Reference	
Absent	7.91 (0.57–108.81)	
Hypothyroidism		0.576
Present	Reference	
Absent	0.48 (0.03–6.21)	
MV at baseline		0.001
Present	Reference	
Absent	25.90 (4.99–134.30)	
Study drug		0.707
Tocilizumab	Reference	
Itolizumab	1.3 (0.32–5.2)	
Remdesivir	2.85 (0.05–15.9)	0.428
Plasma therapy	0.61 (0.21–4.5)	0.532
PO_2/FiO_2 ratio at baseline	0.97 (0.94–0.99)	0.023
TLC	1.06 (0.97–1.17)	0.183
Ferritin	1.00 (1.00–1.00)	0.970
LDH	1.00 (1.00–1.00)	0.777
CRP	0.99 (0.99–1.00)	0.791
D-dimer	1.12 (0.80–1.55)	0.500
IL-6	1.00 (1.00–1.00)	0.387
Procalcitonin	1.55 (0.69–3.46)	0.282

OR: odds ratio; CI: confidence interval; CKD: chronic kidney disease; CAD: coronary artery disease; MV: mechanical ventilation; PO_2: partial pressure of oxygen; FiO_2: fraction of inspiratory oxygen concentration; TLC: total leucocyte count; LDH: lactate dehydrogenase; CRP: C-reactive protein; IL: interleukin.

(24)=78.64, P<0.001) and explained 62.2% of the variation of CI (Nagelkerke R^2). The independent factors significantly affecting CI were comorbidities, MV before administration of the

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study drugs, and baseline PO$_2$/FiO$_2$ ratio (Table 4). The odds of CI in patients without comorbidities were 24.66 times the odds of CI in patients with comorbidities. The odds of CI in patients on oxygen therapy were 25.90 times the odds of CI in patients on MV before study drug administration. There was no significant difference among the baseline parameters (comorbidities, baseline MV, and baseline PO$_2$/FiO$_2$ ratio) that significantly affected the CI between the two groups (Table 1).

Kaplan-Meier survival plots for the two drugs to estimate CI and death at 60 days were plotted (Figures 2 and 3). The estimated median time for CI was 12 days and 11 days in the tocilizumab and itolizumab groups, respectively, which was not significantly different (log-rank P=0.080) (Figure 2). The estimated median time for death was 13 days and 14 days in the tocilizumab and itolizumab groups, respectively, and the difference was not significant (log-rank P=0.089) (Figure 3).

DISCUSSION

Initial trials on tocilizumab failed to show any mortality benefit [13-15]. These results could be attributed to small sample sizes, exclusion of critically ill patients [14,15], and imbalances in steroid use. The Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial was the largest involving tocilizumab, with 4,116 adults, and revealed a significant mortality benefit with the use of tocilizumab over usual care (31% vs. 35%) [5]. The Randomised Embedded Multi-factorial Adaptive Platform Trial for Community Acquired Pneumonia trial also concluded that, in critically ill COVID-19 patients, treatment with the IL-6

receptor antagonists tocilizumab and sarilumab improved outcomes, including survival [4]. The World Health Organisation recently added tocilizumab to the list of prequalified treatments for COVID-19 [16]. In India, itolizumab was approved for "restricted emergency use" to treat COVID-19 patients [17]. However, the evidence in favor is not conclusive due to the lack of trials and small sample sizes.

A phase II trial in which 20 patients received itolizumab and 10 were controls showed 100% recovery in the treated arm versus 70% in the control arm. There was also a significant improvement in key efficacy parameters of lung function, such as PaO$_2$ and SpO$_2$, without increasing oxygen flow in the itolizumab arm [17]. Two studies evaluating the role of itolizumab on COVID-19 are available on preprint servers. One study shows that a single dose of itolizumab decreased the serum IL-6 levels after 48 hours of administration in 24 moderate to critically ill elderly patients with COVID-19 [18]. Another study concluded that, in 19 moderately ill elderly patients with COVID-19, itolizumab was associated with a significantly reduced risk of admission to the ICU and a 10 times lower risk of death [8]. However, despite positive results in these trials, there is no randomized clinical trial on itolizumab.

The results showed no statistical difference in CI between the two groups, which was the primary outcome of the study. However, the maximum PO$_2$/FiO$_2$ ratio achieved after using the study drugs was significantly higher with itolizumab compared to tocilizumab. The number of days needed to improve PO$_2$/FiO$_2$ ratio was significantly fewer in the itolizumab group. The all-cause mortality at 28 days was significantly lower in
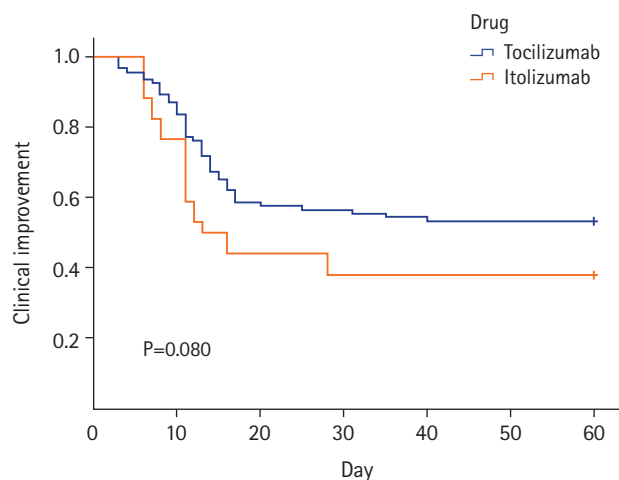
Figure 2. Kaplan–Meier estimate of the cumulative probability of clinical improvement in the treatment group.
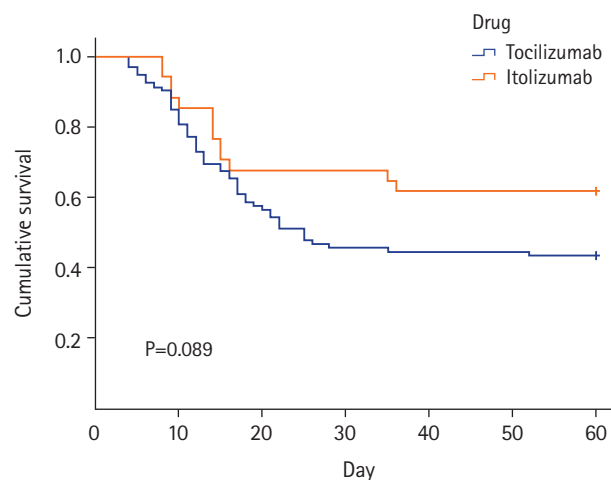
Figure 3. Kaplan–Meier estimate of the cumulative probability of mortality by treatment group.

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itolizumab compared to tocilizumab (32.3% vs. 54.3%). However, the difference in all-cause mortality at 60 days was not significantly different (38.2% vs. 56.5%). This might be due to dilution of the potential effects of the study drugs and confounding factors during prolonged ICU stay. The patients with higher IL-6 values (>30 pg/ml) showed significantly better CI and lower mortality with itolizumab compared to tocilizumab. This signifies that patients with higher IL-6 values responded better to itolizumab.

The results of the RECOVERY trial showed a 28-day mortality of 31% in the tocilizumab group. The higher mortality in our study might be due to a greater percentage of patients on MV before the start of treatment and a longer assessment time of 60 days. In our study, 67% of patients in the tocilizumab group were on MV, whereas 54% of those in the RECOVERY trial were on MV. A case series on 20 patients treated with itolizumab showed a mortality rate of 35% in patients with moderate COVID-19 ARDS compared to 60% in those who had not been treated with an IL-6 inhibitor [10]. In one study, only one death occurred in 19 elderly patients with moderate COVID-19 treated with itolizumab [9]. The results of these two cohorts cannot be compared due to differences in baseline characteristics, study design, management protocols, and quality of care. As severe COVID-19 has a longer course, we followed patients for a longer duration to reduce exclusions.

The median time to discharge was 20 days in both groups, similar to the findings of the RECOVERY trial. The number of patients weaned from MV in our study was about 17% in both groups. The RECOVERY trial showed similar proportions of patients weaned from MV in the tocilizumab and control group (35% vs. 31%). As our study did not include a control group, it is difficult to conclude whether IL-6 inhibitors benefit patients who are already on invasive MV at the time of drug administration.

The time needed to improve the PO_2/FiO_2 ratio was significantly shorter with itolizumab than with tocilizumab (6 vs. 8 days). The best PO_2/FiO_2 ratio achieved after therapy was also significantly better with itolizumab. No large trial on tocilizumab (REMAP-CAP or RECOVERY) has evaluated the effect on the PO_2/FiO_2 ratio.

The incidence of serious adverse effects was significantly higher with itolizumab. Two patients had severe bronchospasm and desaturation after the administration of itolizumab. A high number of adverse events occurred with itolizumab, even after premedication with hydrocortisone and pheniramine. Both cases of bronchospasm occurred with the lyo-

philized form of itolizumab.

Multivariate logistic regression analysis was performed to determine the confounding variables affecting our primary outcome. We found comorbidities, baseline MV, and baseline PO_2/FiO_2 ratio as the factors affecting the CI. However, these confounding factors were distributed equally between the two groups. There was no significant difference in the survival plots for CI or mortality between the two groups. The RECOVERY trial has found significant mortality benefits of 4% with tocilizumab compared to the control group (31% vs. 35%). We found better CI and survival rates with itolizumab, with a difference of 15% and 18%, respectively, compared to tocilizumab. Although the difference was large, it did not reach a significant level due to the small sample size. However, this difference is clinically significant in routine practice.

Our study has some limitations. First, it was a retrospective single-center study. Second, it was not a randomized comparison, so unmeasured confounding variables cannot be ruled out. Third, the use of the study drugs depended on the diagnosis of cytokine storm syndrome at the discretion of the clinician with no objective criteria. Thus, the baseline parameters might not match between the two groups. Fourth, the sample size of our study was small. The itolizumab group had fewer patients because the drug recently was approved for use, and the clinicians lacked experience in using it compared to tocilizumab. Fifth, we did not include a control group in our study. Sixth, it is difficult to consider all adverse effects of the drugs due to the numerous factors affecting the clinical features of a critically ill patient. This might have led to less reporting of adverse drug effects. In addition, in the multivariate analysis, many variables were adjusted, which might have led to the overfitting of the model.

Our study also has strengths. First, it is the first study to compare itolizumab with tocilizumab in the treatment of COVID-19. Second, the follow-up period was long, and we calculated 60-day mortality considering the longer stay of patients with COVID-19 in the ICU. Third, we collected data on daily changes in the PO_2/FiO_2 ratio, demonstrating a significant secondary outcome.

The CI with itolizumab is similar to that of tocilizumab. Itolizumab had a 28-day mortality benefit over tocilizumab but did not at 60 days. Better oxygenation can be achieved with itolizumab, which can be a substitute for tocilizumab in managing severe COVID-19. Large randomized controlled trials to compare the two drugs are needed.

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CONFLICT OF INTEREST

FUNDING

ACKNOWLEDGMENTS

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Effects of ketamine on the severity of depression and anxiety following postoperative mechanical ventilation: a single-blind randomized clinical trial in Iran

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Background: In this study, we compare the effects of ketamine and the combination of midazolam and morphine on the severity of depression and anxiety in mechanically ventilated patients after discharge from the intensive care unit (ICU).

Methods: This randomized single-blind clinical trial included 50 patients who were candidates for craniotomy and postoperative mechanical ventilation in the ICU of 5 Azar Teaching Hospital in Gorgan City, North Iran, from 2021 to 2022. Patients were allocated to two groups by quadruple block randomization. In group A, 0.5 mg/kg of ketamine was infused over 15 minutes after craniotomy and then continued at a dose of 5 μ/kg/min during mechanical ventilation. In group B, midazolam was infused at a dose of 2–3 mg/hr and morphine at a dose of 3–5 mg/hr. After patients were discharged from the ICU, if their Glasgow Coma Scale scores were ≥14, Beck's anxiety and depression inventories were completed by a psychologist within 2 weeks, 2 months, and 6 months after discharge.

Results: The mean scores of depression at 2 months (P=0.01) and 6 months (P=0.03) after discharge were significantly lower in the ketamine group than in the midazolam and morphine group. The mean anxiety scores were significantly lower in the ketamine group 2 weeks (P=0.006) and 6 months (P=0.002) after discharge.

Conclusions: Ketamine is an effective drug for preventing and treating anxiety and depression over the long term in patients discharged from the ICU. However, further larger volume studies are required to validate these results.

Key Words: anxiety; depression; intensive care unit; ketamine; midazolam

INTRODUCTION

As intensive care unit (ICU) care can be accompanied by severe psychological stress in patients [1], millions of ICU survivors live with new-onset mental issues that have short- or long-term consequences leading to reductions in patients' quality of life [2]. Egerod et al. [3]

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reported that 23%–48% and 17%–43% of discharged ICU patients had symptoms of anxiety and depression, respectively. Wu et al. [4] also reported in 2018 that 10%–17% of discharged ICU patients experienced symptoms of depression, anxiety, and stress. Hatch conducted a large-scale prospective cohort study of 21,633 ICU patients hospitalized after trauma and reported that of the remaining 4,943 patients in the study, 46%, 40%, and 22% showed symptoms of anxiety, depression, and stress, respectively [5]. Intensivists have sought to improve the outcomes of such patients through interventions such as physiotherapy [6], post-ICU counseling clinics, and rehabilitation and cognitive therapy programs [7]. Unfortunately, despite extensive efforts, the rates of patient improvement have not been significant [8].

However, pharmacological approaches such as ketamine infusions are promising, but are not well evaluated. As an anesthetic induction drug with strong effects on the glutamate system of the central nervous system, ketamine effectively blocks the N-methyl-D-aspartate (NMDA) receptor and is a very strong pain killer [9]. In addition, this drug has rapid antidepressant effects and is used in the treatment of major and chronic depression [6].

As ketamine is simultaneously a strong pain controller and sedative, we predicted that its administration would reduce the use of additional analgesics and sedatives that are associated with worse clinical and mental outcomes. There are a few studies [10,11] about the positive effects of ketamine on postoperative depression and anxiety, but they focus mostly on short term effects. This study was conducted to compare the effects of ketamine on the severity of depression and anxiety with those of a combination of midazolam and morphine in mechanically ventilated post-craniotomy patients from treatment in the ICU until 6 months after discharge.

MATERIALS AND METHODS

This study was approved from the Ethics and Research Committee of Golestan University of Medical Sciences (No. IR.GOUMS.REC.1399.318). The study was a single-blind randomized clinical trial that entered the implementation stage after obtaining permission from the Ethics Committee of Golestan University of Medical Sciences and registration in the IRCT system (IRCT20170413033408N5). Before registration, all participants read and signed a written informed consent form. A copy of the signed consent form was given to each participant. The guidelines on research involving the use of human

subjects (beneficence, non-maleficence, veracity, confidentiality, and voluntarism) were strictly adhered to in accordance with the Helsinki Declaration. Participants did not incur any cost by participating in this study and there was no financial inducement.

The study population included 18- to 60-year-old patients who were hospitalized for craniotomy to treat non-traumatic brain lesions (such as brain tumors, non-traumatic intracerebral hemorrhage, and hydrocephalus) in the neurosurgery department of 5 Azar Teaching Hospital, Gorgan City, North Iran. The exclusion criteria included people suffering from drug poisoning, patients with suicidal attempts, receiving cardiopulmonary resuscitation, with cerebral dementia and Alzheimer's, or with extensive cerebral hemorrhage. In addition, patients were required to have received at least 48 hours of mechanical ventilation after craniotomy in the ICU. We also excluded cases with confirmation of brain damage and encephalopathy, cardiac arrest, and CPR during hospitalization and treatment of the patient in the hospital, Glasgow Coma Scale (GCS) <14/15 at the time of discharge from the ICU, and withdrawal of consent from this study.

For included patients, an anesthesiologist visited each patient the day before surgery, fully explained the purpose of this study, and obtained written consent to participate in the study. The participants were assigned to either the ketamine group (intervention group) or the midazolam and morphine group (control group) using a four-way block randomization method. Allocation of groups was performed by the anesthesiologist. The anesthesiologist and medical staff who took care of the participants were not blinded to the assigned groups. However, the participants, the psychologist, and the test evaluator were blinded to group allocation.

The ketamine group received with intravenous ketamine (0.5 mg/kg) within 15 minutes after admission to the ICU while remaining intubated. Following the loading dose, ketamine was infused at a dose of 5 μ/kg/min continuously for at least 48

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hours and at the most until extubation. In the midazolam and morphine group, an infusion of 2–3 mg/hr midazolam and 3–5 mg/hr morphine was used to sedate the participants while receiving mechanical ventilation. In both groups, a bolus of 10 to 20 mg propofol was used as a rescue sedative. After extubation and discharge of the patient from the ICU, if the GCS score was ≥14 and the patient was able cooperate by answering questions, she/he would be referred to the psychiatric clinic for an interview. The first interview was a face-to-face interview by a psychologist, 2 weeks after being discharged from the ICU. The second and third interviews were conducted by telephone 2 months and 6 months after discharge. While collecting each patient's demographic information, the duration of mechanical ventilation and the length of stay in the ICU were also collected in a checklist designed for this purpose.

Diagnosis of Mental Disorder
The severities of depression and anxiety were evaluated based on the Beck inventory. Both inventories have 21 questions, with total scores ranging from 0 to 63. In the depression questionnaire, scores of 0–9 indicate the absence of depression, scores of 10–18 indicate mild to moderate depression, scores of 19–29 indicate moderate to severe depression, and scores of 30–63 indicate severe depression. In the anxiety questionnaire, scores of 0–7 indicate no or very low anxiety, scores of 8–15 indicate mild anxiety, scores of 16–25 indicate moderate anxiety, and scores of 26–63 indicate severe anxiety [12]. Ghassemzadeh et al. [13] confirmed the validity and reliability of the Beck depression questionnaire in the Iranian context in a study in 2005, and Salari-Moghaddam confirmed the validity and reliability of the Beck anxiety questionnaire in Iran in a study in 2018 [14].

Statistical Analysis
The quantitative and qualitative data are presented as mean values (standard deviation) and frequency (percentage), respectively. Independent Student t-tests were used to compare the means in the two groups and analysis of variance was used for three or more groups. Repeated measures analysis of variance was used for simultaneous intra-group and inter-group inferences. P-values <0.05 were considered statistically significant. Stata version 12 (Stata Corp.) was used for all statistical analyses. Sample size was calculated with G*Power software version 3.1.9.4 using the mean and standard deviation of the results of Ionescu et al. [15]. Based on an effect size of d=0.821, a power of 80%, and a two-sided α risk of 5%, 56 patients were required (28 per arm) including dropouts.

RESULTS

In this study, 56 patients who underwent craniotomy at 5 Azar Teaching Hospital in Gorgan City, North Iran, were subjected to postoperative mechanical ventilation in the ICU (Figure 1). We included 25 patients in each group who were able to cooperate until the end of the study and whose data were subjected to statistical analysis. The demographic characteristics of the study participants are shown in Table 1. Most of the patients in the ketamine group (59%) and in the control group (68%) were male, and this difference was not statistically significant (P=0.37). The variables of height, weight, body mass index, underlying diseases, underlying psychiatric history, and type of surgery were not significantly different between the two groups. The length of stay in the ICU and the duration of mechanical ventilation received by the patients are shown in Table 1. Here, too, the differences between the two groups were not statistically significant.

As shown in Table 2 and Figure 2, in patients who received ketamine, the mean scores for the depression severity test at 2 weeks, 2 months, and 6 months after discharge from the ICU were 22 vs. 25 (P=0.28), 16 vs. 20 (P=0.01), and 8 vs. 11 (P=0.03) and the control group, respectively. The mean anxiety scores of the two groups are shown in Table 3 and Figure 3. At 2 weeks, 2 months, and 6 months after discharge from the ICU, the scores were 23 vs. 31 (P=0.006), 21 vs. 23 (P=0.09), and 10 vs. 14 (P=0.002) in the ketamine group and the control group, respectively.

Repeated measures analysis of variance was used to evaluate the effect of time on the severity of depression and anxiety, as shown in Table 4. With the passage of time, the mean scores of anxiety and depression disorders in both groups of patients gradually decreased. Given that the prerequisite of sphericity was not met in this study (P=0.008), the Greenhouse Geisser method was used for analyses. The effect on the study group also became significant, indicating that depression and anxiety scores in the two groups receiving ketamine and a combination of midazolam and morphine were significantly different after controlling for the effect of time. The non-significance of the interaction coefficient between time and group type (P=0.71) for the variable of depression indicates that both the passage of time and the type of treatment had no significant effect on patients depression scores.

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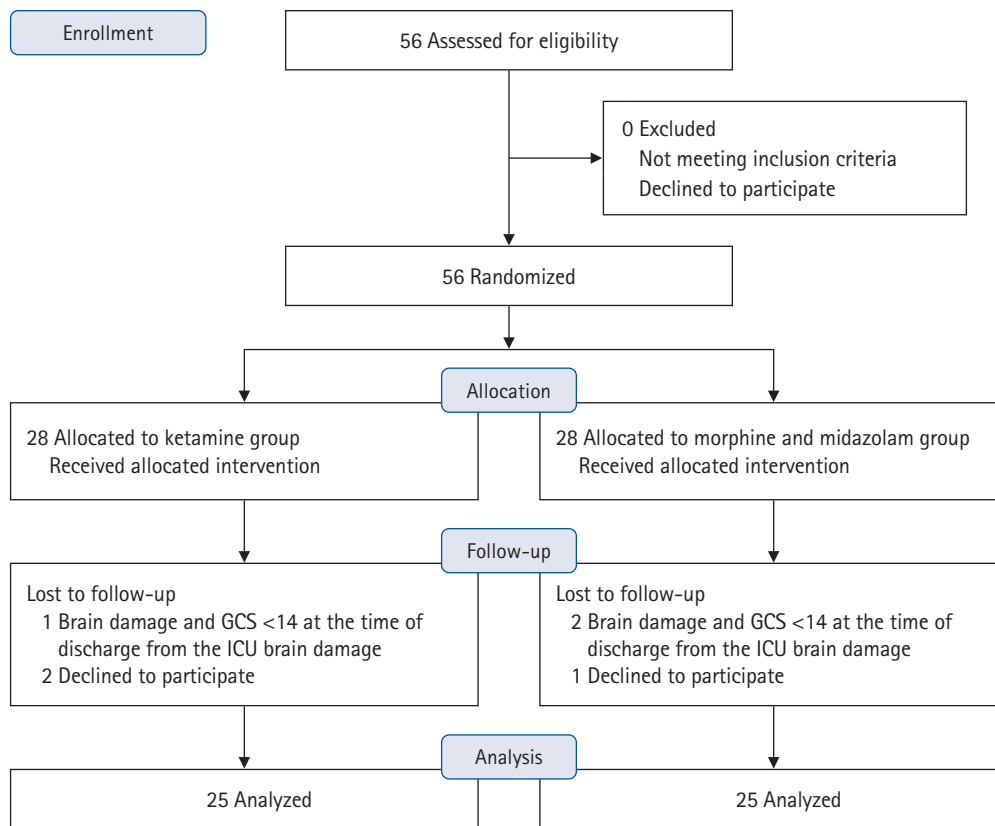
Figure 1. Consolidated Standards of Reporting Trials (CONSORT) diagram of patient recruitment. GCS: Glasgow Coma Scale; ICU: intensive care unit.

Table 1. Demographic characteristics of participants

Variable	Ketamine group (n=25)	Midazolam and morphine group (n=25)	P-value
Age (yr)	57±15	53±13	0.92[a]
Height (cm)	175±12	177±12	0.66[a]
Weight (kg)	79±19	79±18	0.90[a]
Body mass index (kg/m^2)	26±9	25±10	0.94[a]
Length of stay in the ICU (day)	6±4	6±5	0.65[a]
Duration of mechanical ventilation (day)	3±2	4±4	0.24[a]
Male	14 (56)	17 (68)	0.37[b]
Underlying disease			0.51[b]
Diabetes mellitus	10 (40)	12 (48)	
Hypertension	11 (44)	13 (52)	
Cerebral vascular diseases	9 (36)	10 (40)	
Others	5 (20)	6 (24)	
Underlying psychiatric history	4 (16)	3 (12)	0.63[b]
Type of surgery			0.32[b]
Brain tumor	10 (40)	11 (44)	
Nontraumatic intracerebral hemorrhage	5 (20)	6 (24)	
Hydrocephalus	6 (24)	5 (20)	
Others	4 (16)	3 (12)	

Values are presented as mean±standard deviation or number (%).
a) Independent t-test; b) Chi-square test.

Table 2. Comparison of the scores of depression of two groups

Time	Ketamine group (n=25)	Midazolam and morphine group (n=25)	P-value
Depression 2 weeks after discharge	22±8	25±7	0.28
Depression 2 months after discharge	16±5	20±5	0.01[a]
Depression 6 months after discharge	8±5	11±4	0.03[a]

Values are presented as mean±standard deviation.
a) Independent t-test.

Table 3. Comparison of the mean scores of anxiety of two groups

Time	Ketamine group (n=25)	Midazolam and morphine group (n=25)	P-value
Anxiety 2 weeks after discharge	23±10	31±8	0.006[a]
Anxiety 2 months after discharge	21±4	23±3	0.09
Anxiety 6 months after discharge	10±3	14±4	0.002[a]

Values are presented as mean±standard deviation.
a) Independent t-test.

Table 4. Results of analysis of variance for repeated measurements of depression and anxiety scores in participants

Outcome variable	Effects	Mean square	F	P-value
Depression	Time effect (within-subjects contrasts)	68.01	4.20	0.040[a]
	Group effect (between-subjects effects)	315.27	5.37	0.020[a]
	Interaction effect of time and group (within-subjects contrasts)	2.18	0.13	0.710
Anxiety	Time effect (within-subjects contrasts)	136.74	8.84	0.005[a]
	Group effect (between-subjects effects)	628.36	13.08	0.001[a]
	Interaction effect of time and group (within-subjects contrasts)	106.90	6.91	0.012[a]

a) Independent t-test.
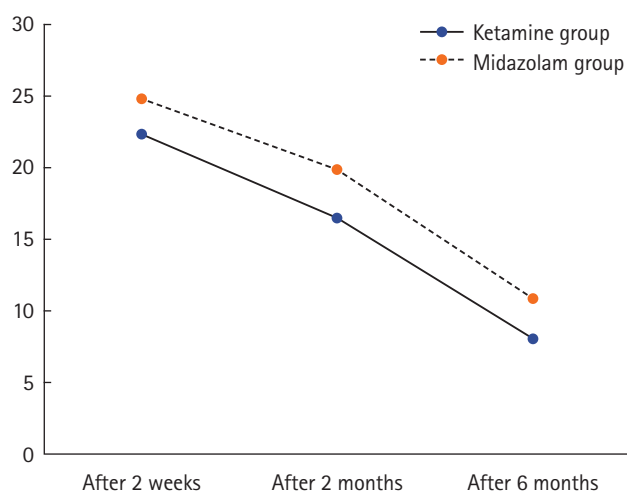
Figure 2. Changes in depression scores in the 6 months after discharge from the intensive care unit.
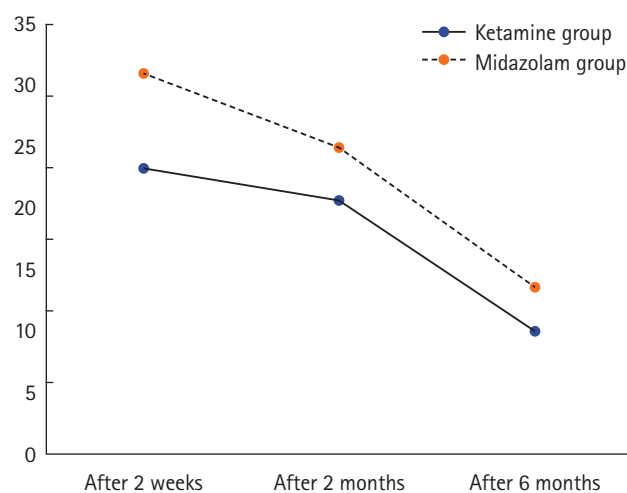
Figure 3. Changes in anxiety scores in the 6 months after discharge from the intensive care unit.

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DISCUSSION

In this study, we found that the use of ketamine as the drug of choice for sedation of mechanically ventilated patients in the ICU is associated with promising results for the reduction of anxiety and depression. There are multiple hypotheses explaining the mechanism of action of ketamine as an antidepressant agent, including direct synaptic or extra-synaptic (GluN2B-selective) NMDAR inhibition, selective inhibition of NMDARs localized on GABAergic interneurons, and the role of α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor (AMPAR) activation [16,17]. Duman et al. [18] suggested that ketamine induces firing of GABA interneurons, resulting in glutamate bursts. Deyama and Duman [19] showed that ketamine rapidly increases brain-derived neurotrophic factor release and hippocampal neurogenesis. Zanos and Gould [16] found in 2018 that the proposed mechanisms of ketamine's antidepressant actions are not mutually exclusive and may in fact complement each other to result in the unique antidepressant effects of the drug. Indeed, a net result of all these processes is a sustained potentiation of excitatory synapses in cortico-mesolimbic brain circuits involved in the maintenance of mood and stress-reactivity. There are additional mechanisms including ketamine's effects on the monoaminergic systems, as well as its anti-inflammatory actions, which are postulated to be involved in the mechanisms underlying its antidepressant actions.

Previous studies have evaluated the effects of ketamine on prevention and treatment of patients with depression, with contradictory results observed. Zarate et al. observed that ketamine infusion could elicit a rapid and significant antidepressant response in patients with bipolar depression and rapidly improve suicidal thoughts in these patients [20]. However, Niciu et al. [21] found in 2013 that, at a subanesthetic dose, ketamine did not change mood in people with treatment-resistant major depression . In a study of 26 patients with major depression and suicidal thoughts, Ionescu et al. [15] observed that six infusions of 0.5 mg/kg ketamine over 45 minutes had no effect compared to placebo three months after treatment and did not reduce the symptoms of depression.

The primary objective of the present study is to evaluate the preventive effect of ketamine against depression and anxiety after craniotomy in patients without histories of depression or anxiety disorders. Several previous studies addressed the controversial effects of ketamine on postoperative depression. In 2023, Gan et al. [11] discussed the effect of esketamine on the occurrence of depressive symptoms in patients undergoing thoracoscopic lung cancer surgery. In that study, 156 patients received ketamine infusion during and 48 hours after surgery. Normal saline was administered to the control group and Beck's questionnaire was used to evaluate results. They found that depressive symptoms decreased 1 month after the operation [11]. In 2023, Zhang et al. [10] examined Crohn's patients undergoing intestinal resection treated with ketamine at a dose of 0.25 mg/kg as an intravenous drip and then with a dose of 0.12 mg/kg/hr. In the control group, 0.9% saline was used. In that study, low-dose ketamine reduced mild to moderate depressive symptoms without the risk of severe side effects [10].

In a review study, Pang et al. [22] evaluated 13 articles with 1,148 patients. According to their results, (R, S)-ketamine was no different from placebo in reducing depression after spinal and general anesthesia. On the other hand, in a meta-analysis of nine randomized clinical trials, Wang et al. [23] measured the effects of intravenous ketamine on depressive symptoms in 2,468 post-surgical patients, finding that ketamine had positive effects on reducing depressive symptoms despite the emergence of side effects. Similarly, in this study we used a 0.5 mg/kg ketamine bolus dose at the end of the operation, and 5 μ/kg/min infusion during at least 48 hours of postoperative mechanical ventilation. Based on our results, when administered in the form of a bolus and then an infusion, ketamine can reduce depression scores 2 and 6 months after treatment in patients discharged from the ICU compared to the control group. However, ketamine treatment was not successful in controlling depression 2 weeks after discharge or for controlling the occurrence of acute depression.

Fewer studies have been conducted evaluating the effects of ketamine on anxiety. In a systematic review in 2022, Tully et al. [24] showed that ketamine could be effective for improving anxiety, but the effect was temporary and after 2 weeks anxiety scores returned to the baseline level. In 2019, Glue et al. [25] investigated the effect of ketamine on patients with treatment-resistant generalized anxiety disorder and social anxiety disorder. Twelve patients were treated with increasing doses of ketamine (0.25, 0.5, 1 mg/kg) at weekly intervals. In the control group, midazolam was used at a dose of 0.01 mg/kg. The results of that survey indicated positive effects of ketamine for reducing anxiety symptoms [25].

There were a few limitations in the present study. First, the sedatives used in the control group were midazolam and lorazepam, which are the most commonly used benzodiazepines in ICU patients [26]. However, Hsu et al. [27] showed in 2015 that

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sedation with midazolam can lead to selective cognitive impairment or the prolongation of such impairment in patients. Therefore, the appropriate response of patients in this study to ketamine may be due to the lack of midazolam in these patients. In order to address this bias, we required that patients have a GCS score higher than 14 after being discharged from the ICU. Second, we were unable to obtain baseline depression and anxiety scores for patients. Therefore, we ensured that there were no between-group differences in psychiatric history. Third, this study was conducted in single center. Multiple randomized prospective trials worldwide are required to validate the results of this study.

In conclusion, in this study we found that ketamine was effective for reducing the severity of anxiety and depression, particularly in the long term, after ICU treatment. Our results suggest that ketamine is a treatment option for mental disorders in this patient population, but further research is needed to fully understand its short-term effects and confirm its efficacy. This study highlights the importance of timely intervention and appropriate drug therapy for addressing mental health issues in critically ill patients and emphasizes the need for continued research in this area.

CONFLICT OF INTEREST

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

FUNDING

ACKNOWLEDGMENTS

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AUTHOR CONTRIBUTIONS

Conceptualization: SM, FT. Data curation: SG, SM, HS. Formal analysis: FM. Methodology: SM, FT, SM, HS, RS. Project administration: SM. Visualization: SG. Writing–original draft: SM, FT, SG, FM. Writing–review & editing: all authors.

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Are sodium-glucose co-transporter-2 inhibitors associated with improved outcomes in diabetic patients admitted to intensive care units with septic shock?

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Background: Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have been shown to reduce organ dysfunction in renal and cardiovascular disease. There are limited data on the role of SGLT2i in acute organ dysfunction. We conducted a study to assess the effect of SGLT2i taken prior to intensive care unit (ICU) admission in diabetic patients admitted with septic shock.
Methods: This retrospective cohort study used electronic medical records and included diabetic patients admitted to the ICU with septic shock. We compared diabetic patients on SGLT2i to those who were not on SGLT2i prior to admission. The primary outcome was in-hospital mortality, and secondary outcomes included hospital and ICU length of stay, use of renal replacement therapy, and 28- and 90-day mortality.
Results: A total of 98 diabetic patients was included in the study, 36 in the SGLT2i group and 62 in the non-SGLT2i group. The Sequential Organ Failure Assessment and Acute Physiology and Chronic Health Evaluation III scores were similar in the groups. Inpatient mortality was significantly lower in the SGLT2i group (5.6% vs. 27.4%, P=0.008). There was no significant difference in secondary outcomes.
Conclusions: Our study found that diabetic patients on SGLT2i prior to hospitalization who were admitted to the ICU with septic shock had lower inpatient mortality compared to patients not on SGLT2i.

Key Words: intensive care unit; mortality; septic shock, sodium-glucose cotransporter-2 inhibitor; type 2 diabetes mellitus

INTRODUCTION

Septic shock represents about two percent of all hospital admissions in the United States, with inpatient mortality rates around 29% [1]. Other than antimicrobial therapy, targeted therapies that reduce mortality in septic shock are limited [2,3]. A recent study dapagliflozin in patients with cardiometabolic risk factors hospitalised with COVID-19 (DARE-19) evaluated the use of sodium-glucose cotransporter-2 inhibitors (SGLT2i) in acutely ill patients. In 2021, this randomized controlled clinical trial investigated the use of the SGLT2i dapagliflozin in

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patients hospitalized with coronavirus disease-19 (COVID-19) [4]. As SGLT2i medications have become part of the mainstay therapy in heart failure and chronic kidney disease (CKD) in addition to diabetes, the authors theorized that SGLT2i may have potential organ-protective effects in acute illnesses such as COVID-19 [5-8]. Although the study did not find a significant difference in organ dysfunction or death, the medications were well tolerated [4]. Another study by Angé et al. [9] showed a potential mechanistic protective effect of SGLT2i in mouse models with capillary leak syndrome. The researchers demonstrated that canagliflozin acts by counteracting lipopolysaccharide-induced vascular leak in mice.

Although these protective effects have been observed in specific organ dysfunction, studies evaluating the use of SGLT2i in shock, simultaneously affecting multiple organ systems, are lacking. Our study aimed to evaluate whether SGLT2i medications were associated with improved outcomes in diabetic adults admitted to the intensive care unit (ICU) with septic shock.

MATERIALS AND METHODS

Setting and Population
We conducted a retrospective cohort study to compare outcomes in diabetic adult patients (18 years or older) on SGLT2i and admitted to the ICU for septic shock to those in diabetic adults who were not on SGLT2i at the time of admission. The Institutional Review Board of Mayo Clinic (ID 22-000810) approved the study on February 2, 2022. The requirement for written informed consent was waived for this minimal-risk study. Procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975.

An electronic medical record review identified the study cohort using International Classification of Diseases codes, 10th and 9th revisions (ICD-10 and ICD-9) such as R65.21 (severe sepsis with septic shock) and 785.52 (septic shock), respectively. The patient pool was narrowed to those who had been diagnosed with type 2 diabetes mellitus. The medication lists of the diabetic patients with septic shock were reviewed to identify those prescribed SGLT2i. The SGLT2i group included only patients prescribed SGLT2i as part of their outpatient medication list within 48 hours of admission to ICU for septic shock. Other exclusion criteria were other etiologies of shock, post-surgical patients admitted in the immediate postoperative period to the ICU, and patients transferred from an outside facility and

KEY MESSAGES

- Our study found an association between sodium-glucose cotransporter-2 inhibitors (SGLT2i) use prior to admission and reduced inpatient mortality in diabetic patients with septic shock.
- Large prospective studies are needed to assess the potential mortality benefit of SGLT2i use in septic shock.

insufficient records (Figure 1).

Data Collection
The electronic medical record collected baseline data about demographics, clinical characteristics, use of anti-hyperglycemic agents and other preadmission medications, hemoglobin A1c within 12 months of admission, source of infection, and type of vasopressor used. The Acute Physiology and Chronic Health Evaluation (APACHE) III and Sequential Organ Failure Assessment (SOFA) scores were recorded as well as the types of SGLT2i used. The primary outcome of the study was in-hospital mortality, and secondary outcomes included hospital and ICU length of stay, use of renal replacement therapy, and 28- and 90-day mortality.

Data Analysis Strategy
The study used R software version 4.1.2 (R Foundation for Statistical Computing) to conduct analyses. Continuous variables were examined with histograms and summarized using median and interquartile range. Categorical variables were described using frequencies and proportions. Due to the
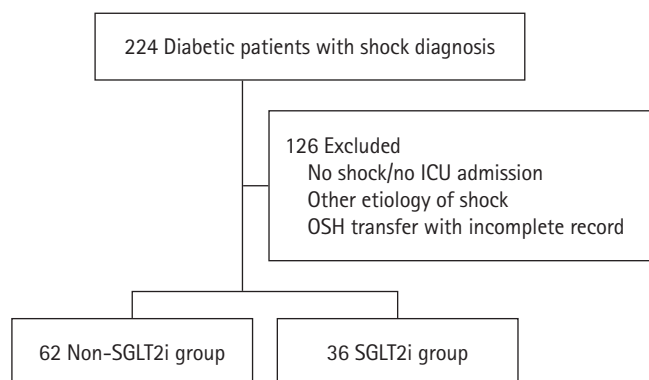
Figure 1. Flowchart for patient selection. ICU: intensive care unit; OSH: outside hospital; SGLT2i: sodium-glucose cotransporter-2 inhibitors.

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non-normal distribution of the variables, differences between SGLT2i patients and non-SGLT2i were obtained using median and chi-square tests. A value of P <0.05 determined statistical significance for all tests.

RESULTS

Baseline Characteristics

A total of 98 diabetic patients admitted to the ICU with septic shock was included in the study. Sixty-two patients (63.3%) were not on SGLT2i, and 36 (36.7%) were on therapy with an SGLT2i prior to hospital admission. The dates of hospitalization ranged between years 2014 and 2022.

Most of the demographics, baseline characteristics, and medication use were similar between the two groups (Table 1). The median ages of SGLT2i and non-SGLT2i cohorts were 68 and 70 years, respectively. There were more male patients in the SGLT2i group, 72.2% versus 58.1% of females, but this difference was not significant. Body mass index was similar in the two groups. Because of the small sample size of individuals with ethnicity other than White (n=8), the study combined all other groups into a single category, with no difference in ethnicities between the SGLT2i and non-SGLT2i groups. Glucagon-like peptide-1 agonists, metformin, and angiotensin-converting enzyme inhibitors were more frequently used in the SGLT2i group. Patients in the SGLT2i group had higher median hemoglobin A1c (7.8 vs. 7, P=0.026). There was also a difference in the sources of infection between the two groups. Close to half of the patients in non-SGLT2i group had a gastrointestinal source of infection compared to only 16.7% of the SGLT2i group. A large portion (30.6%) of the patients in the SLGT2i group had other sources of infection such as bacteremia, followed by those with a pulmonary origin. There was a difference between the two groups in the presence of CKD and coronary artery disease (CAD). CKD was more common in the non-SGLT2i group (38.7% vs. 11.1%, P=0.004), while CAD was more common in the SGLT2i group (33.3% vs. 14.5%, P=0.029). Illness severity scores of SOFA and APACHE III were similar between the two groups. Phenylephrine was more frequently used in the SLGT2i group (16.7 % vs. 3.2%, P=0.019). The types and numbers of SGLT2i users are shown in Table 2.

Outcomes

The primary outcome of in-hospital mortality was significantly lower in the SGLT2i group compared to the non-SGLT2i group (5.6% vs. 27.4%, P=0.008). The difference at 28 and 90 days was not significant. There was no difference between the two

Table 1. Patient demographics and baseline characteristics

Variable	SGLT2i group (n=36)	Non-SGLT2i group (n=62)	P-value
Age (yr)	68 (62–72)	70 (58–78)	0.140[a]
Sex			0.161[b]
Male	26 (72.2)	36 (58.1)	
Female	10 (27.8)	26 (41.9)	
Race			0.417[b]
White	32 (88.9)	58 (93.5)	
Other	4 (11.1)	4 (6.5)	
BMI (kg/m^2)	29.9 (16.5–51.3)	29.5 (19.1–51.3)	0.677[a]
Comorbid condition			
CAD	12 (33.3)	9 (14.5)	0.029[b]
CKD	4 (11.1)	24 (38.7)	0.004[b]
Hypertension	30 (83.3)	44 (71.0)	0.170[b]
Infection source			0.004[b]
Gastrointestinal	6 (16.7)	29 (46.8)	
Pulmonary	8 (22.2)	14 (22.6)	
Other[c]	11 (30.6)	5 (8.1)	
Urinary	7 (19.4)	8 (12.9)	
Unknown	2 (5.6)	6 (9.7)	
Cutaneous	2 (5.6)	0	
Medication			
ACEi	23 (63.9)	25 (40.3)	0.024[b]
β-Blocker	17 (47.2)	31 (50.0)	0.791[b]
Statin	25 (69.4)	35 (56.5)	0.203[b]
Insulin	16 (44.4)	22 (35.5)	0.380[b]
Metformin	19 (52.8)	11 (17.7)	<0.001[b]
Sulfonylureas	7 (19.4)	10 (16.1)	0.676[b]
GLP-1 agonist	9 (25.0)	2 (3.2)	<0.001[b]
Thiazolidinedione	2 (5.6)	1 (1.6)	0.275[b]
DPP-4	3 (8.3)	1 (1.6)	0.105[b]
Aspirin	12 (33.3)	21 (33.9)	0.957[b]
Hemoglobin A1c[d]	7.8	7	0.026[a]
SOFA score	9.5 (7.8–11.0)	9.0 (7.0–11.0)	0.214[a]
APACHE III score	75.5 (65.0–94.5)	73.5 (60.3–102.0)	0.878[a]
Vasopressor			
Norepinephrine	35 (97.2)	58 (93.5)	0.426[b]
Vasopressin	14 (38.9)	23 (37.1)	0.860[b]
Phenylephrine	6 (16.7)	2 (3.2)	0.019[b]
Epinephrine	3 (8.3)	1 (1.6)	0.105[b]
Dopamine	0	2 (3.2)	0.276[b]

Values are presented as median (interquartile range) or number (%).
SGLT2i: sodium-glucose cotransporter-2 inhibitor; BMI: body mass index; CAD: coronary artery disease; CKD: chronic kidney disease; ACEi: angiotensin-converting enzyme inhibitor; GLP-1: glucagon-like peptide-1agonist; DPP-4: dipeptidyl peptidase 4; SOFA: Sequential Organ Failure Assessment; APACHE: Acute Physiology and Chronic Health Evaluation.
a) Median test; b) Chi-square test; c) Bacteremia, central nervous system infection, amputation infection; d) Hemoglobin A1c was recorded if was available in electronic record and completed within 12 months of hospital admission.

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Table 2. Types of SGLT2i taken by the cohort

SGLT2i type	Patient (n=36)
Empagliflozin	23 (63.9)
Dapagliflozin	8 (22.2)
Canagliflozin	5 (13.9)

Values are presented as number (%).
SGLT2i: sodium-glucose cotransporter-2 inhibitor.

Table 3. Study outcomes

Variable	SGLT2i group (n=36)	Non-SGLT2i group (n=62)	P-value
Hospital length of stay	7.5 (4.8–12.3)	9.2 (4.8–12.0)	0.40[a]
ICU length of stay	2.8 (2.1–4.0)	2.9 (1.7–5.3)	0.40[a]
Inpatient mortality	2 (5.6)	17 (27.4)	0.008[b]
28-Day mortality	7 (19.4)	22 (35.5)	0.094[b]
90-Day mortality	13 (36.1)	25 (40.3)	0.680[b]
RRT	4 (11.1)	13 (21.0)	0.214[b]

Values are presented as median (interquartile range) or number (%).
SGLT2i: sodium-glucose cotransporter-2 inhibitor; ICU: intensive care unit; RRT: renal replacement therapy.
[a]Median test; [b]Chi-square test.

groups in either hospital or ICU length of stay. Additionally, there was no difference in renal replacement therapy rates between the two cohorts. Table 3 summarizes the study outcomes.

DISCUSSION

Our retrospective cohort study evaluating the role of SGLT2i in ICU outcomes of diabetic patients admitted for septic shock found an association between diabetic patients taking SGLT2i and lower in-hospital mortality compared to diabetic patients not on SGLT2i. The lack of hospital mortality reduction at 28 and 90 days could be related to study withdrawal or discontinuation of SGLT2i at the time of admission.

Although the study cohort was small, these findings are consistent with the known organ protective effect and mortality reduction seen with SGLT2i in patients with CKD and heart failure [5-8]. Although there were some differences in baseline characteristics such as CKD and CAD, the APACHE III and SOFA scores were similar in the groups, suggesting that they were equal in their illness severity at the time of admission to the ICU.

One of the only clinical trials to test the hypothesis of an impact of SGLT2i on reducing organ dysfunction and mortality in acutely ill patients is the DARE-19 trial [4]. This double-blind, randomized, placebo-controlled 1:1 trial analyzed the impact of dapagliflozin on patients admitted to the hospital with COVID-19. The primary outcomes included a composite of time to new or worsening organ dysfunction (respiratory, cardiovascular, and renal decompensation) and death from any cause. Treatment with SGLT2i did not significantly reduce organ dysfunction in this study. The mortality rates were lower in the SGLT2i group (6.6% vs. 8.6%; hazard ratio, 0.77; 95% confidence interval, 0.52–1.16), but the difference was not statistically significant. Though the authors anticipated higher rates of organ dysfunction and death, they believe that the improvements in COVID-19 treatment played a role in the lower-than-expected events.

Possible mechanistic explanations for the benefit of SGLT2i in shock include improved energy metabolism and reduced inflammation through interleukin (IL)-1β andIL-6 [9-11]. Angé et al. [9] also identified a potential mechanism by which SGLT2i may reduce capillary leakage. Lipopolysaccharide O55:B5 (LPS) was injected into mice pretreated with a clinically relevant dose of canagliflozin. The study demonstrated that canagliflozin reduced LPS-induced myocardial edema and prevented albuminemia. The mechanism they identified was canagliflozin activation of the AMP-activated protein kinase (AMPK) pathway resulting in the reinforcement of inter-endothelial junctions [9]. They tested this hypothesis further with the treatment of human mammary epithelial cells with plasma from both healthy volunteers and septic shock patients. Canagliflozin showed preservation of vascular endothelial cadherin integrity [9]. Several other potential beneficial mechanisms of SGLT2i have been identified. For example, in human endothelial cells, canagliflozin has been shown to reduce pro-inflammatory cytokines IL-1β-mediated secretion of IL-6 and monocyte chemoattractant protein-1 [11]. These mediators are well known to play a role in the pathophysiology of sepsis [12].

Renal impairment in septic shock is an important consideration when discussing initiation of SGLT2i. Several studies have evaluated the use of SGLT2i after a certain reduction in estimated glomerular filtration rate (eGFR). The Dapagliflozin in Patients with Chronic Kidney Disease (DAPA-CKD) trial evaluated the effects of dapagliflozin in patients with CKD with and without diabetes. The trial included 4,304 participants, 624 with eGFR <30. The primary composite outcome was sustained decline in eGFR of at least 50%, end-stage renal disease, and death from renal or cardiovascular events. The results were persistent regardless of eGFR, with significantly lower rates of primary outcomes in patients treated with dapagifloz-

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in [6,13]. A more recent trial published by the EMPA-Kidney Collaborative Group evaluated the effect of empagliflozin on the progression of CKD. A total of 6,609 patients was enrolled, with 2,282 (34.5%) having eGFR <30. Like the DAPA-CKD trial, progression of CKD and death from cardiovascular causes occurred at significantly lower rates (13.1% vs. 16.9%) in the empagliflozin group compared to the placebo group. These benefits were consistent regardless of eGFR [8]. The evidence for patients with eGFR <25 is limited, and current trials are enrolling patients to evaluate the safety and efficacy of cana-gliflozin and dapagliflozin in patients with CKD stages 4 and 5. Current Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend use of SGTL2i in patients with eGFR >20 until dialysis or transplant [14].

The safety profile of SGLT2i has been extensively studied. Fournier's gangrene was initially of concern as a serious complication of SGLT2i use. However, a more recent meta-analysis of 42,415 patients on SGLT2i found no difference in rates of Fournier's gangrene, cellulitis, or erysipelas [15]. The early concerns for increased rates of urinary tract infections have also been evaluated, revealing no association [6,8,13].

SGLT2i are associated with euglycemic diabetic ketoacidosis (DKA) in patients with type 1 diabetes mellitus, at rates of 4%–6% [13]. However, the rates of DKA are much lower in patients with type 2 diabetes mellitus and have occurred at similarly low rates in recent CKD studies [6,8,13]. In the DARE-19 trial, DKA occurred only in two patients receiving dapagliflozin and was reported as non-severe, resolving after medication discontinuation [4].

We acknowledge the limitations of this retrospective analysis. Due to the small sample size and the small number of events (e.g., deaths), regression analysis could not be performed to account for some of the baseline differences (CAD and CKD). SGLT2i are typically discontinued on admission, and the half-life of most ranges between eight to 16 hours [16]. Therefore, the impact of SGLT2i on outcomes may be blunted in our study. However, the cellular signaling and downstream effects could potentially persist and could be a theoretical explanation for the decreased inpatient mortality. Inherent limitations of a retrospective analysis such as limitations of medical records, lack of ability for stringent patient selection, and inability to randomize, all apply to our study. However, SOFA and APACHE III scores were used to assess patient illness severity and were similar in the two cohorts.

We found a significant association of lower in-hospital mortality in septic shock in diabetic patients taking a SGLT2i at the time of ICU admission. Although there were several limitations to this retrospective study, our findings suggest that SGLT2i could provide a beneficial effect in this patient population. Larger studies are needed to confirm this association and to understand the beneficial effects of these drugs in septic shock patients.

CONFLICT OF INTEREST

FUNDING

ACKNOWLEDGMENTS

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Implementation of Society for Cardiovascular Angiography and Interventions classification in patients with cardiogenic shock secondary to acute myocardial infarction in a spanish university hospital

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Background: Killip-Kimball classification has been used for estimating death risk in patients suffering acute myocardial infarction (AMI). Killip-Kimball stage IV corresponds to cardiogenic shock. However, the Society for Cardiovascular Angiography and Interventions (SCAI) classification provides a more precise tool to classify patients according to shock severity. The aim of this study was to apply this classification to a cohort of Killip IV patients and to analyze the differences in death risk estimation between the two classifications.

Methods: A single-center retrospective cohort study of 100 consecutive patients hospitalized for "Killip IV AMI" between 2016 and 2023 was performed to reclassify patients according to SCAI stage.

Results: Distribution of patients according to SCAI stages was B=4%, C=53%, D=27%, E=16%. Thirty-day mortality increased progressively according to these stages (B=0%, C=11.88%, D=55.56%, E=87.50%; P<0.001). The exclusive use of Killip IV stage overestimated death risk compared to SCAI C (35% vs. 11.88%, P=0.002) and underestimated it compared to SCAI D and E stages (35% vs. 55.56% and 87.50%, P=0.03 and P<0.001, respectively). Age >69 years, creatinine >1.15 mg/dl and advanced SCAI stages (SCAI D and E) were independent predictors of 30-day mortality. Mechanical circulatory support use showed an almost significant benefit in advanced SCAI stages (D and E hazard ratio, 0.45; 95% confidence interval, 0.19–1.06; P=0.058).

Conclusions: SCAI classification showed superior death risk estimation compared to Killip IV. Age, creatinine levels and advanced SCAI stages were independent predictors of 30-day mortality. Mechanical circulatory support could play a beneficial role in advanced SCAI stages.

Key Words: cardiogenic shock; Killip-Kimball; mechanical circulatory support; myocardial infarction; Society for Cardiovascular Angiography and Interventions classification

Original Article

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INTRODUCTION

Cardiogenic shock (CS) is one of the deadliest critical cardiac conditions, with a 30-day death rate of 30%–50% [1-4]. CS is mainly caused by acute myocardial infarction (AMI) and occurs in about 5%–10% of patients suffering from AMI [1]. The Killip-Kimball classification has been broadly used to determine the clinical situation and to estimate prognosis [5]. Patients who develop cardiogenic shock secondary acute myocardial infarction cardiogenic shock (AMICS) have stage IV of this classification. However, the cardiogenic shock spectrum is wide and implies different prognoses along it. The Society for Cardiovascular Angiography and Interventions (SCAI) classification was first published in 2019, defining five stages of cardiogenic shock according to severity. Stage "A" stands for "At risk" and involves a patient who potentially could develop cardiogenic shock (e.g., anterior ST-elevation myocardial infarction with left ventricular dysfunction) but is not currently experiencing signs or symptoms. Stage "B" stands for "Beginning" and involves a patient who is decompensated (tachycardia and hypotension without hypoperfusion). Stage "C" stands for "Classic" and refers to a patient that meets the classic cardiogenic shock criteria, showing hypoperfusion signs and requiring vasoactive support or even mechanical circulatory support (MCS) to achieve stabilization. Stage "D" stands for "deteriorating" and involves a patient who could not be stabilized with initial therapies and maintains a hypoperfusion status and requires additional measures to reverse the condition (e.g., additional drugs or MCS). Finally, stage "E" stands for "Extremis" and involves a patient in deep shock, frequently in refractory cardiac arrest or supported by several MCS devices and drugs [6]. This classification was updated in 2022 to include some modifications in the cut-offs used to define the stages (e.g., lactate, hemodynamic parameters) [7]. An illustrative chart with complete criteria for SCAI classification is provided in Supplementary Figure 1.

Despite several studies validating the use of SCAI classification in patients with CS due to different causes, no prior studies have evaluated the difference in mortality estimation between the Killip IV classification and the different SCAI stages in an AMICS population [8-10].

MATERIALS AND METHODS

We retrospectively analyzed the last 100 patients who experienced cardiogenic shock admitted to the acute cardiac care unit of our hospital with a Killip IV AMI diagnosis between January 2016 and October 2023. Our center is a tertiary hospital with a 24-hour available cath-lab and cardiac surgery team but with no long-term assist devices or heart transplantation program. No extracorporeal cardiopulmonary resuscitation (e-CPR) program was operative during the study period.

Cardiogenic shock was defined as systolic blood pressure ≤90 mm Hg maintained for at least 30 minutes and a cardiac index ≤2.2 L/min/m^2 or need for vasoactive drugs or mechanical support to achieve systolic blood pressure or cardiac index above the cut-off level, according to the definition provided by the National Cardiovascular Data Registry [11]. Exclusion criteria included all types of non-AMI-derived cardiogenic shock and missing data that prevented reclassification in SCAI stages.

Patient demographics and comorbidities; angiographic, echocardiographic, and analytic parameters (peak values during hospitalization); systolic blood pressure at admission; vasoactive index score (VIS); orotracheal intubation or mechanical ventilation; mechanical support; and type of mechanical support were included in this study. Temporal trends associated with mechanical support and its influence on patient prognosis were explored (two time periods were compared: before and after year 2020).

We retrospectively classified these patients in different SCAI stages according to the criteria proposed by the 2022 SCAI SHOCK Stage Classification Expert Consensus Update [7]. The VIS calculation was performed according to the formulae indicated in Belletti et al. [12] (Supplementary Table 1).

The study protocol was approved by the Ethics Committee of Badajoz University Hospital Complex (No. CEI 032/23) and

KEY MESSAGES

- The Society for Cardiovascular Angiography and Interventions (SCAI) classification provides more precise information about shock severity and showed better mortality estimation than Killip-Kimball (stage IV) classification.
- Older age, renal function impairment and advanced SCAI stages (D and E) are significant predictors of 30-day mortality in cardiogenic shock secondary to myocardial infarction.
- Use of mechanical circulatory support could help to improve the prognosis of patients with advanced SCAI stages.

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was conducted in accordance with the Declaration of Helsinki. Due to the retrospective character of the study, informed consent waiver was authorized by the local ethics committee.

Statistical Analysis

Categorical variables are presented as frequencies (percentages). Normal distribution was explored using the Shapiro-Wilk test. Because most continuous variables did not follow a normal distribution, they are presented as medians and interquartile ranges (IQRs) for uniformity. Differences in categorical variables among SCAI stages were analyzed using the Fischer exact test. The Mann-Whitney U-test for non-normally distributed variables was used to assess differences. Differences in continuous variables among SCAI stages were explored via the Kruskal-Wallis test. Thirty-day survival was analyzed using the Kaplan-Meier method, and comparisons among groups were explored using the log-rank test. Hazard ratio (HR) and 95% confidence interval (CI) values for 30-day mortality

were explored using univariate Cox regression models. Cut-off points for continuous variables for inclusion in the model were determined using the Liu index. Variables that showed a P-value <0.1 were introduced in a multiple Cox regression model to explore significant 30-day mortality predictors. A two-tailed P-value <0.05 was considered statistically significant.

RESULTS

Study Population

The median patient age was 66 years (IQR, 54–77 years), and 68% of patients were male (Table 1). Upon admission, 87% of patients presented with ST-elevation myocardial infarction, and 86.4% of these patients underwent percutaneous coronary intervention as a first attempt at revascularization, while 13.6% received fibrinolysis. Of these, 91.67% were submitted for rescue PCI. Median systolic blood pressure at admission was 80.0 mm Hg (IQR, 70.0–90.0 mm Hg). Median lactate level

Table 1. Demographic, clinical, analytical and echocardiographic features among different SCAI stages

Variable	Killip IV (n=100)	SCAI				P-value
		B (n=4)	C (n=53)	D (n=26)	E (n=17)	
Demographic feature						
Male (%)	68.0	50.0	71.7	61.5	70.6	0.67
Age (yr)	66 (54–77)	65 (60–68)	63 (54–75)	71 (50–80)	67 (54–78)	0.97
HTN (%)	50.0	25.0	43.4	61.5	58.8	0.31
DLP (%)	37.0	75.0	39.6	23.1	41.2	0.16
DM (%)	28.0	25.0	20.8	30.8	47.1	0.19
Smoking habit (%)	39.0	75.0	49.1	23.1	23.5	0.10
Clinical, analytical and echocardiographic features						
SBP (mm Hg)	80.0 (70.0–90.0)	72.5 (60.0–92.0)	85.0 (80.0–95.0)	74.5 (69.0–90.0)	75.0 (70.0–80.0)	0.03
Creatinine (mg/dl)	1.3 (0.9–2.0)	0.9 (0.8–1.0)	1.1 (0.8–1.4)	1.7 (1.3–2.6)	3.1 (1.9–4.6)	<0.001
AST (UI/L)	331.5 (114.0–557.0)	121.5 (91–211.0)	183.0 (69.0–426.5)	456.0 (111.0–724.0)	460.0 (371.0–1,256.0)	0.01
Lactate (mmol/L)	3.5 (1.9–6.5)	1.7 (1.7–1.7)	2.4 (1.9–3.5)	5.5 (3.8–8)	7.0 (6.0–12.5)	<0.001
LVEF (%)	30.0 (20.0–41.0)	50.0 (47.5–55.0)	35.0 (25.0–40.0)	30.0 (25.0–43.5)	20.0 (15.0–22.5)	<0.001
VIS	20.0 (10.0–55.0)	10.0 (10.0–10.0)	12.5 (8.0–20.0)	65.0 (22.0–98.5)	79.5 (45.7–120.9)	<0.001
OTI (%)	60.0	25.0	52.8	61.5	88.2	0.02
OTI length (hr)	48 (24–96)	24 (24–24)	48 (24–96)	48 (24–96)	48 (24–96)	0.68
MCS (%)	20.0	0	11.3	30.8	35.3	0.05
IABP (%)	15.0	0	7.6	30.8	17.7	0.05
ECMO (%)	4.0	0	0	11.5	5.9	0.07
Impella (%)	5.0	0	2.2	0	17.7	0.10
LVEF at discharge (%)	40 (32–50)	58 (55–60)	45 (35–50)	35 (25–45)	15 (10–30)	<0.001
Length of stay (day)	7.9 (2.3–14.4)	5.3 (4.7–5.8)	9.4 (6.2–13)	3.1 (1.2–16.2)	2.3 (0.8–6.0)	0.03

Values are presented as median (interquartile range).
SCAI: Society for Cardiovascular Angiography and Interventions; HTN: hypertension; DLP: dyslipidemia; DM: diabetes mellitus; SBP: systolic blood pressure; AST: aspartate aminotransferase; LVEF: left ventricle ejection fraction; VIS: vasoactive index score; OTI: orotracheal intubation; MCS: mechanical circulatory support; IABP: intra-aortic balloon pump; ECMO: extracorporeal membrane oxygenation.
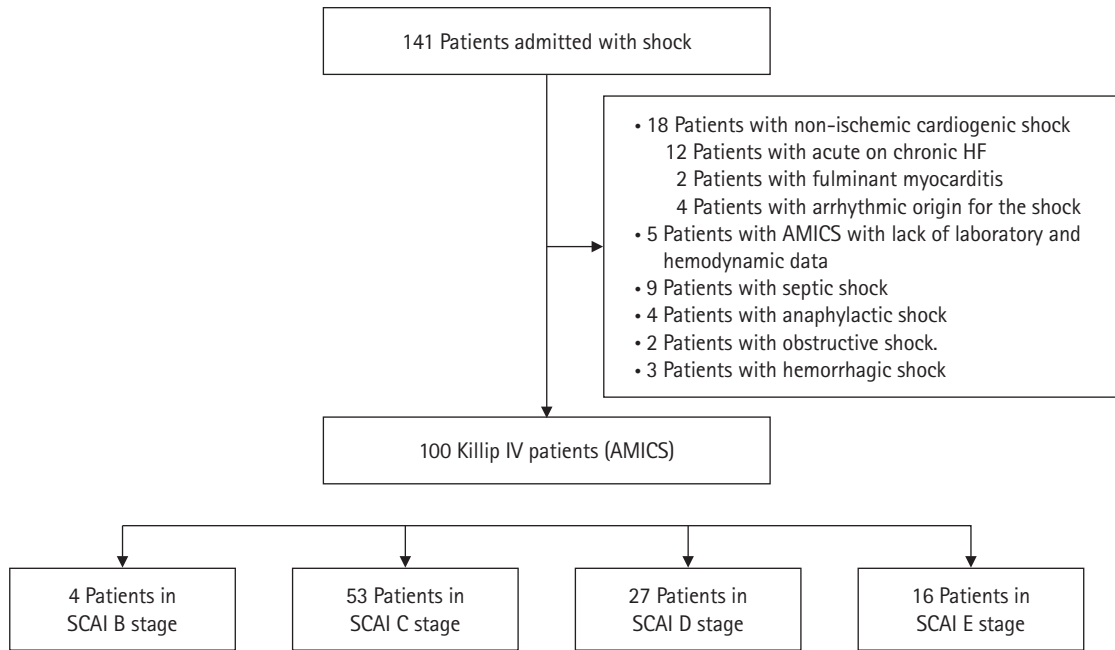
Figure 1. Patient inclusion flowchart. HF: heart failure; AMICS: acute myocardial infarction cardiogenic shock; SCAI: Society for Cardiovascular Angiography and Interventions.

was 3.5 mmol/L (IQR, 1.93–6.49 mmol/L). Median creatinine value was 1.33 mg/dl (IQR, 0.94–2 mg/dl). Median aspartate aminotransferase (AST) was 331.5 IU (IQR, 114–557 IU). Median VIS was 20 (IQR, 10–55). Additionally, 60% of patients required orotracheal intubation and invasive mechanical ventilation with a median ventilation time of 48 hours (IQR, 24–96 hours). Median left ventricle ejection fraction (LVEF) was 30% (IQR, 20%–41%). MCS was used in 20% of patients. Use of MCS increased greatly when comparing 2016–2020 to 2020–2023 (12.16 vs. 42.31%, P=0.001). Distribution of patients according to SCAI stage was B=4%, C=53%, D=27%, and E=16% (Figure 1).

Analysis of 30–Day Mortality

The 30-day death rate was 35% when patients were classified only as Killip IV AMI. As expected, 30-day mortality increased progressively according to SCAI stage (B=0%, C=11.88%, D=55.56%, E=87.50%; log-rank test P<0.001) (Figure 2). Subgroup analysis comparing mortality between Killip IV and established shock SCAI stages (C, D and E) showed significant differences, indicating that Killip IV classification overestimated risk mortality in SCAI C patients (35% vs. 11.88%, log-rank test P=0.002) and underestimated risk mortality in SCAI D and E (35% vs. 55.56% and 87.50%, respectively; log-rank test P=0.03 and P<0.001, respectively) (Figure 3).

Cut-off points for continuous variables were determined us-
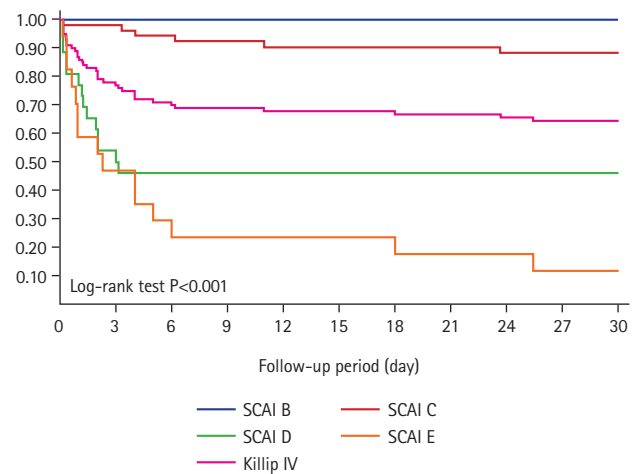
Figure 2. Kaplan-Meier plot showing progressive increase in 30-day mortality rate according to Society for Cardiovascular Angiography and Interventions (SCAI) stage and Killip IV stage.

ing the Liu index as follows: age >69 years, VIS score >20, arterial lactate >3.5 mmol/L, creatinine >1.15 mg/dl, AST >200 IU/L, and LVEF <20%. Univariate Cox regression showed that all variables had a significant or near significant association with 30-day mortality, advanced SCAI stage (D and E), and previous history of diabetes mellitus. Older age (over 69 years: HR, 2.34; 95% CI, 1.15–4.86; P=0.019), slightly elevated creat-

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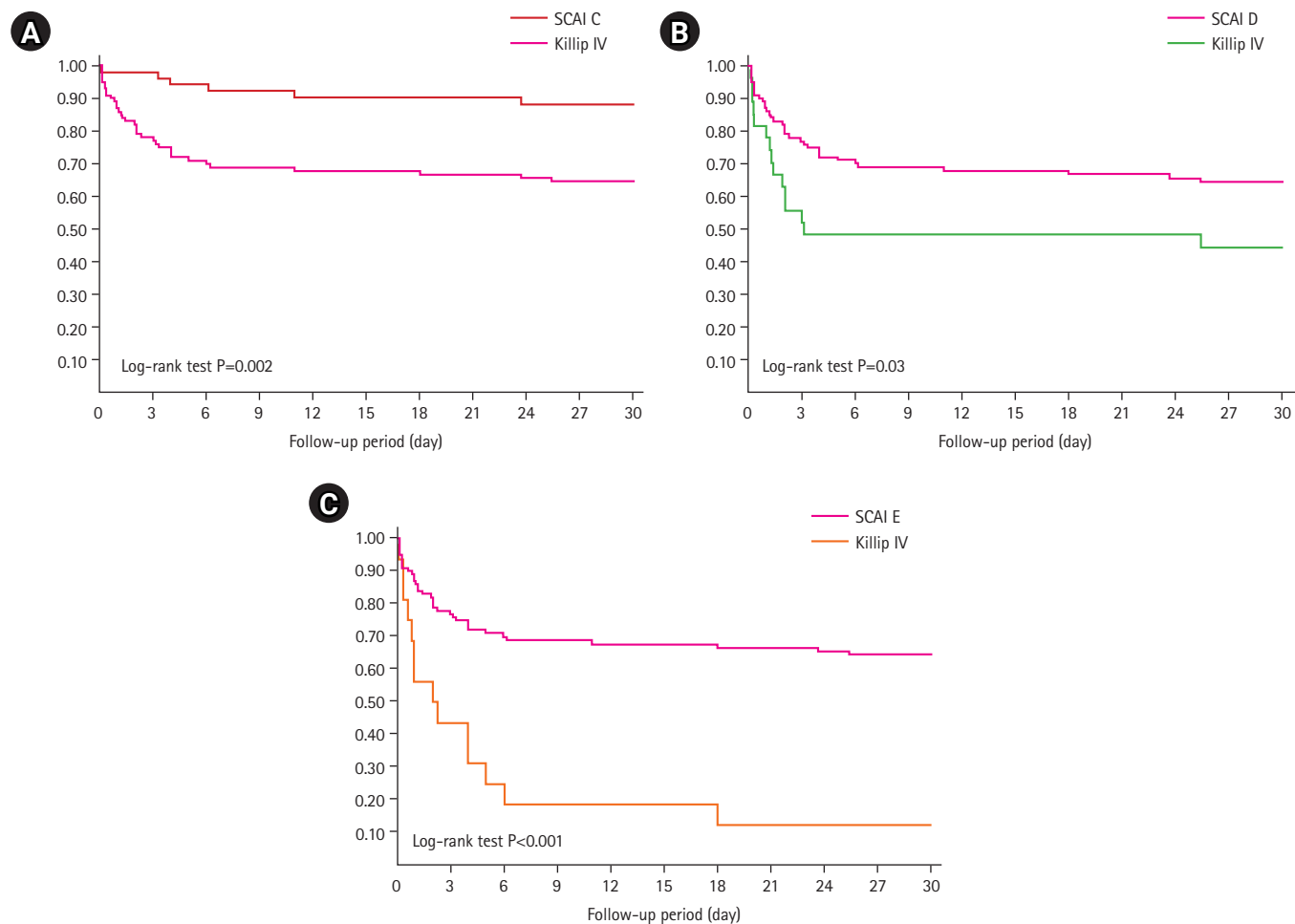
Figure 3. Comparison of 30-day mortality rate estimation between Killip IV stage and Society for Cardiovascular Angiography and Interventions (SCAI) C (A), D (B), and E (C) stages.

Table 2. 30-Day mortality predictors for patients in cardiogenic shock

Variable	Univariate Cox regression		Multiple Cox regression	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age >69 yr	2.95 (1.48–5.86)	0.002	2.34 (1.15–4.76)	0.019
Diabetes mellitus	1.39 (0.99–1.95)	0.056	–	-
AST >200 IU/L	2.39 (1.08–5.27)	0.031	-	-
VIS >20	4.31 (1.67–11.12)	0.003	-	-
Lactate >3.5 mml/L	10.16 (2.43–42.40)	0.001	-	-
Creatinine >1.15 mg/dl	30.43 (4.16–222.55)	0.001	11.52 (1.43–92.77)	0.022
LVEF <20%	1.95 (0.96 –3.99)	0.067	-	-
SCAI D stage	2.56 (1.30–5.05)	0.007	3.29 (1.20–9.01)	0.020
SCAI E stage	5.73 (2.90–11.32)	<0.001	6.21 (2.28–16.88)	<0.001

HR: hazard ratio; CI: confidence interval; AST: aspartate aminotransferase; VIS: vasoactive index score; LVEF: left ventricle ejection fraction; SCAI: Society for Cardiovascular Angiography and Interventions.

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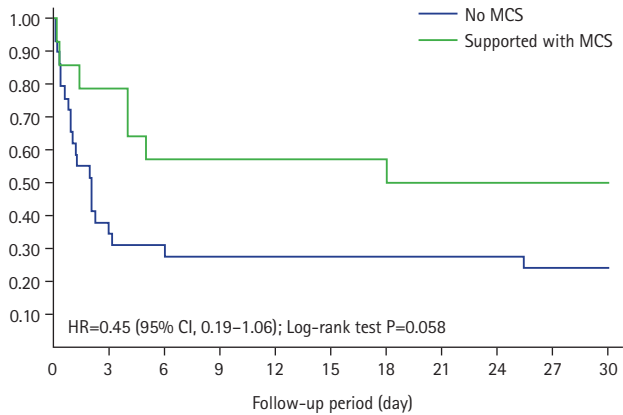
Figure 4. Kaplan–Meier curves showing impact of mechanical circulatory support (MCS) on survival in advanced Society for Cardiovascular Angiography and Interventions (SCAI) stages. HR: hazard ratio; CI: confidence interval.

inine (creatinine >1.15 mg/dl: HR, 11.52; 95% CI, 1.43–92.77; P=0.022), and advanced SCAI stage (SCAI D: HR, 3.29; 95% CI, 1.20–9.01; P=0.020 and SCAI E: HR, 6.21; 95% CI, 2.28–16.88; P<0.001) were significant predictors of 30-day mortality (Table 2).

Impact of MCS

No significant global benefit was observed from MCS use (P=0.92). However, when we analyzed the impact of MCS in patients with advanced SCAI stages (D and E), a nearly significant benefit was observed (HR, 0.45; 95% CI, 0.19–1.06; log-rank test P=0.058) (Figure 4). This trend was not seen in the other stages.

Patients with MCS presented with lower LVEF (25.63 vs. 33.36%, P=0.023), worse liver function (AST: 857.2 vs. 400.4 IU, P= 0.012), and a nearly significantly worse kidney function (creatinine levels: 2.43 vs. 1.75 mg/dl, P=0.061). Patients who were assisted with MCS also needed more support with vasoactive drugs and higher doses (VIS score: 108.5 vs. 31.56, P<0.001). As SCAI classification stage increased, MCS use increased (0% for SCAI B, 11.32% for SCAI C, 30.77% for SCAI D, and 35.29% for SCAI E; P=0.048). No significant differences in age were found among the SCAI stages, although patients that were assisted with MCS tended to be younger than patients who were not assisted (61.35 vs. 66.99 years, P=0.099).

DISCUSSION

It is established that SCAI classification improves the ability to estimate death risk in cardiogenic shock patients and can

be a useful tool to titrate patient's therapeutic needs [8,9]. In this cohort of 100 patients who developed AMICS, classifying patients only as Killip IV led to an overestimation of mortality compared to SCAI C stage (35% vs. 11.88%, P=0.002) and an underestimation when compared to SCAI D and E stages (35% vs. 55.56% and 87.50% respectively, P=0.03 and P<0.001, respectively). These findings should encourage physicians to use SCAI classification in AMICS patients as the reference prognosis stratification tool and to abandon the outdated solitary concept of Killip IV AMI in these highly complex patients. In addition, we showed that advanced SCAI stages (D and E) were strong predictors of 30-day mortality, which was consistent with several previous findings in which mortality increased with shock severity according to SCAI classification [9,10,13,14].

Distribution of patients according to SCAI stage was similar to the observed in Jentzer et al. [15], except that this work had a larger number of SCAI B patients, in contrast to the predominant SCAI C stage observed in our study. Similarity in number of patients in stages D and E was noted with the 2020 study from Schrage et al. [9]; and the summary of the SCAI A, B, and C patients of that study is very similar to that of our SCAI C patients. These differences could be explained by lack of consideration of SCAI A or most SCAI B patients as Killip IV. The distribution observed in Hanson et al. was also similar to ours [10].

Use of MCS varies widely. A study by Schrage et al. [16] showed 13% of MCS use in a large cohort of 441,696 patients with cardiogenic shock treated in German hospitals between 2005 and 2017. The use of MCS was higher in the AMICS cohort, raising up to 20.15%. Intra-aortic balloon pump (IABP) was the most frequently used device (16.19%), followed by veno-arterial extracorporeal membrane oxygenation (VA-ECMO; 2.31%) and percutaneous left ventricular assist device (pLVAD) (1.65%). This is similar to the MCS use observed in our study [16]. Kim et al. [17] also reported 23% of MCS use. In a recent study from Berg et al. [18], a cohort of patients without invasive hemodynamic assessment in the first 24 hours of admission showed a MCS distribution similar to ours (IABP, 17.6%; Impella, 5.5%; ECMO, 4.2%). However, other studies have found higher MCS use. For example, Jentzer et al. [15] reported 43.5% MCS use in their two-center study, which nearly matches the 42.31% MCS use found in our work for the 2020–2023 period. This increase in MCS use was probably related to the introduction of pLVAD and ECMO devices in our center in 2020. Use of MCS increased according to shock

severity, and ECMO and pLVAD were the most used devices in SCAI E stage. We observed a huge increase in MCS use in this stage when comparing the two study periods (10% vs. 71.43%, P=0.035). IABP was the most frequently used device in C and D stages, very similar to percentages reported in Jentzer et al. [14]. No global benefit was observed from MCS, although we found a near significant reduction in mortality in SCAI D and E patients assisted with MCS, which is encouraging given the lack of data showing a clear beneficial effect derived from their use. A larger sample may have yielded a significant result. On the other hand, our center does not have a heart transplantation program or a long-term assist devices program, as our hospital is not a reference center but a referring hospital, and the volume of patients that would reap a potential benefit from short-term therapies is likely lower than that observed in other national reference hospitals with those programs. This may be a main reason why, along with high mortality rate, the length of stay for SCAI E patients seems considerably short in our cohort, because these patients are referred to national referral hospitals as soon as they are stabilized and there is no sign of early cardiac recovery. The absence of an operative extracorporeal cardiopulmonary resuscitation program in our hospital probably influenced the less frequent use of ECMO in SCAI E patients compared with other studies.

Our study is consistent with previous evidence that identified age and kidney injury as significant predictors of short-term mortality in CS patients [19,20]. The relationship between age and shock severity (according to SCAI stage) has also been explored along with its association with death risk in patients with CS [15]. Age did not show a significant association with worse kidney or liver function, higher lactate levels, or VIS score or SCAI stage in our study (all P>0.05). Thus, other age-related factors such as frailty, reduced biological reserve, or delirium should be considered as possible contributors to worse prognosis in elders [21]. Renal function deterioration has been described as a short-term mortality predictor in CS [22,23]. In a sub-study of the IABP-Shock II-trial, which explored novel renal function biomarkers in AMICs, creatinine level >1.32 mg/dl was the only significant predictor of short-term death in AMICS [24]. This value is similar to the cut-off point obtained in our study. These relatively low numbers could indicate a key role of renal impairment in such patients, even in early stages of deterioration. The recently published work by Zweck et al. [25] showed that patients in cardiogenic shock who developed a cardiorenal profile had a higher mortality rate than those with a non-congested profile but a lower rate than those with a cardiometabolic profile.

Our work has some limitations. First, this is a retrospective observational study, so no definitive causalities should be extracted from it. Second, this is a single-center study with a small sample. However, our findings are consistent with previous evidence and provide some new encouraging data for SCAI classification and MCS use in severely ill patients in cardiogenic shock. Future studies with higher-class evidence and larger samples are needed to confirm our findings. Finally, the characteristics of our hospital—a tertiary hospital with no heart transplantation program, long-term assist devices, or an operative e-CPR program during the study period—probably limit extrapolation of our findings to other centers with similar features. Larger reference centers would include patients with different SCAI stages and a higher or at least different proportion of patients assisted with MCS.

CONFLICT OF INTEREST

FUNDING

ACKNOWLEDGMENTS

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SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4266/acc.2023.01620.

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Catheter detection by transthoracic echocardiography during placement of peripherally inserted central catheters: a real-time method for eliminating misplacement

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Background: Although guidelines and protocols are available for central venous access, existing methods lack specificity and sensitivity, especially when placing peripherally inserted central catheters (PICCs). We evaluated the feasibility of catheter detection in the right atrial cavity using transthoracic echocardiography (TTE) during PICC placement.
Methods: This single-center, retrospective study included consecutive patients who underwent PICC placement between January 2022 and March 2023. TTE was performed to detect the arrival of the catheter in the right atrial cavity. Catheter misplacement was defined as an aberrant catheter position on chest x-ray (CXR). The primary endpoint was predicting catheter misplacement based on catheter detection in the right atrial cavity. The secondary endpoint was optimizing catheter placement and examining catheter-associated complications.
Results: Of the 110 patients identified, 10 were excluded because of poor echogenicity and vein access failure. The remaining 100 patients underwent PICC placement with TTE. The catheter was visualized in the right atrial cavity in 90 patients. CXR exams revealed catheter misplacement in seven cases. Eight patients with catheter misplacement underwent the same procedure in the other arm. In two patients, PICC placement failed due to anatomical reasons. Catheter misplacement was detected using TTE with sensitivity, specificity, positive predictive value, and negative predictive value of 97% confidence interval (CI; 91.31%–99.36%), 90% CI (55.50%–99.75%), 99%, and 75%, respectively.
Conclusions: TTE is a reliable tool for detecting catheter misplacement and optimizing catheter tip positioning during PICC placement.

Key Words: catheterization; echocardiography; peripherally inserted central catheter

INTRODUCTION

Misplacement of peripherally inserted central catheters (PICCs) is a challenging problem. If

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the catheter is not in the correct position after placement, the patient may need to be prepared for another puncture site or the other arm may be required for reinsertion. Precise one-time placement of PICCs is crucial, because patients who undergo this type of procedure are mostly older adults or are frail from extended intravascular administration of medication and nutrition. Many patients experience poor vascular conditions when the available central vein is accessed because they have received intravenous fluid peripherally or centrally for extended periods.

Real-time imaging techniques, including fluoroscopy or the C-arm, are routinely used by PICC practitioners during procedures [1,2]. During PICC placement, patients and medical staff are exposed to radiation through fluoroscopy, but fluoroscopy is a valuable imaging tool for real-time functional and anatomical assessments. The cumulative radiation dose may be as high as >950 mGy or the peak skin dose as >760 mGy [3]. Adverse reactions can occur with the use of contrast agents in fluoroscopic procedures, especially in individuals with kidney disease [4], and patients may need to be relocated to another unit for image-guided interventions.

During central venous catheter (C-line) insertion procedures, most C-lines are inserted percutaneously using the Sedlinger technique. In both C-line and PICC procedures, vessel puncture is routinely performed under ultrasonographic guidance. Transthoracic echocardiography (TTE) is a reliable tool for detecting catheter misplacement and optimizing catheter tip positioning during C-line insertion [5]. When inserted correctly, the PICC is long enough to reach the right atrial cavity. Point-of-care ultrasonography (POCUS) is a pervasive and standard technique for verifying PICC placement using TTE [6]. If an echocardiographic probe and a vessel probe are prepared ahead of time, the procedure can be performed by switching the probes without the need to relocate the patient for the procedure.

The methodological differences between PICC and C-line placement lie in the access area and the extent of catheter-length adjustment according to this area [7,8]. In an environment where the ultrasound system is already prepared, the probes can be easily switched: the cardiac probe is placed on the patient's chest to perform echocardiography. This facilitates the verification of whether the catheter is correctly located on the right side of the heart. Correct guidance prevents the catheter from moving to the opposite arm or neck during PICC placement. Compared to C-arm or fluoroscopy, this method may reduce the total procedure time, patient burden,

KEY MESSAGES

- For high frailty patients who require critical care, moving patients to other locations equipped with fluoroscopy or C-arm devices for peripherally inserted central catheter (PICC) placement can be dangerous and cumbersome.
- When point-of-care ultrasonography is pervasive, bedside transthoracic echocardiography could be a reliable tool for detecting catheter misplacement and optimizing catheter tip positioning during PICC placement.

and health insurance expenses. Additionally, this method uses only ultrasound and no radiation is generated (unlike fluoroscopy or C-arm fluoroscopy) during the procedure.

Several guidelines and protocols are available for central venous access, but there are no data regarding specificity or sensitivity for these methods, particularly when placing PICCs [9-11]. In this study, we aimed to evaluate the utility of periprocedural TTE for predicting PICC positioning.

MATERIALS AND METHODS

This retrospective study was conducted at a single center and included consecutive patients who underwent PICC placement. All patients who underwent PICC implantation performed by a single cardiovascular surgeon between January 2022 and March 2023 were eligible for this study. The primary endpoint was predicting catheter misplacement based on catheter detection in the right atrial cavity. The secondary endpoints were optimizing catheter tip placement in the superior vena cava–right atrium (SVC–RA) junction on chest x-ray (CXR) and examining all catheter-associated complications.

The study protocol was approved by the Chungnam University Hospital Institutional Review Board (No. 2023-04-018). Requirement for informed consent was waived by the Institutional Review Board because of the study retrospective design. Approval for publication was obtained from the patients whose photographs are included in this paper.

Vital signs were assessed before each procedure, and real-time monitoring of electrocardiograms and pulse oximetry saturation was performed for each patient. Punctures were conducted under ultrasonographic guidance, and TTE was performed before and during the procedure. Catheter misplacement was defined as an aberrant catheter position (coiled,

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directed toward the neck or other arm) on peri- or post-procedural CXR.

In this study, two types of catheters were used: (1) 5-Fr polyurethane 3-lumen Pro-PICC (MedComp) and (2) 5-Fr polyurethane 2-lumen Arrowg+ard Blue Advance PICC (Arrow PICC, Teleflex). Multiple ultrasonography devices were employed in various settings, including the intensive care unit, general ward, rehabilitation center, and operating room. These devices included 12L and 3Sc-RS probes (Venue Go Ultrasound System, GE), 11L and 3SP-D probes (Logiq S7 Expert Ultrasound System), UST-5413 linear and UST-5299 cardiac probes (Aloka F31 Diagnostic Ultrasound System, Hitachi), and 12L and 3Sc probes (Vivid S5 Ultrasound System, GE).

Exclusion Criteria

The exclusion criteria were as follows: (1) pre-procedural ultrasonography showing no adequate upper extremity veins during rapid peripheral vein assessment (RaPeVA); (2) poor pre-procedural echocardiographic window with difficulty finding the right atrial cavity; (3) signs of severe infection in the upper extremities; and (4) multiple former PICC puncture failures in both the upper extremities [10].

Ultrasonography and Echocardiography Pre-procedures

All patients had their arms abducted in the supine position and fixed upward if they could not cooperate. First, the operator measured the patient's height and sternal length to calculate the catheter length in advance. A tourniquet was tied as high as possible on the shoulder of the arm selected for the procedure. Prior to the sterile drape, a RaPeVA using a linear probe was performed for the right arm [10]. In cases where the patient's range of arm movement was limited, such as in patients with cerebral infarction, the opposite arm was moved first. The basilic vein in the upper arm was selected as the first target vessel and the brachial vein was identified as the next vessel, considering its size and tortuosity. Blood vessels with diameters ≥2 mm were selected as targets after tying the arm with a tourniquet. When no blood vessel was available in the first arm, the other arm was prepared and draped again. Once the target vessel was determined, the vein access point was pre-marked on the arm to save time and to use in actual procedures (Figure 1A).

TTE was also briefly performed. Each patient was informed that their chest may be pressed before and during the procedure. Similar to the apical four-chamber or subcostal views, the view that best showed the right atrial cavity was selected,

and the chest area where the probe was located was marked. This procedure reduced the difficulty of finding a good view of the right atrial cavity (Figure 1B).

Each patient was informed that a wide surgical drape had been applied during the procedure and the possibility of needing to prepare another arm if necessary was explained in advance. The surgical drapes were applied to the arms and chest in a typical manner. For the echocardiographic window, a surgical drape was prepared with a 10×10 cm hole in the area marked in advance and exposed. Probes were wrapped in a sterile probe cover so that both the echocardiographic and linear probes could be used during the procedure.

PICC Procedure and Real-Time Echocardiography

All PICC procedures started with a puncture in a vein predetermined by RaPeVA, using ultrasonography in real-time. Under observation, 2–3 mL of 1% lidocaine was injected subcutaneously into the puncture site before puncture or after guidewire insertion. The catheter length was predicted and calculated during preparation, but the catheter was not trimmed in advance because when it is trimmed in advance, it may be too short to reach and confirm the right atrial cavity. The PICC was placed in a standard manner using the following catheter detection protocols. (1) If the target vein puncture was successful, a catheter was inserted, with the length calculated in advance, followed by guidewire insertion. (2) When the catheter was fully introduced to the calculated length, whether it was placed correctly in the right atrial cavity was determined using real-time TTE with an echocardiographic probe. (3) If the catheter was placed in the right atrial cavity on TTE, it was withdrawn until the tip was located at the SVC–RA junction. (4) If the catheter was not found in the right atrial cavity, it was retracted and reinserted, and the previous protocol was repeated. (5) If the catheter was not identified in the right atrial cavity again, periprocedural portable CXR was required. (6) If periprocedural portable CXR showed malposition, the procedure was considered to have failed and was then tried in the other arm. (7) If the catheter was placed at the SVC– RA junction on TTE, post-procedural CXR was performed for final confirmation. The practitioner determined the placement of the catheter. The practitioner and patient were kept in the procedure unit until CXR evaluation.

Statistical Analysis

All statistical analyses were performed using IBM SPSS statistics version 26. The sensitivity, specificity, and likelihood

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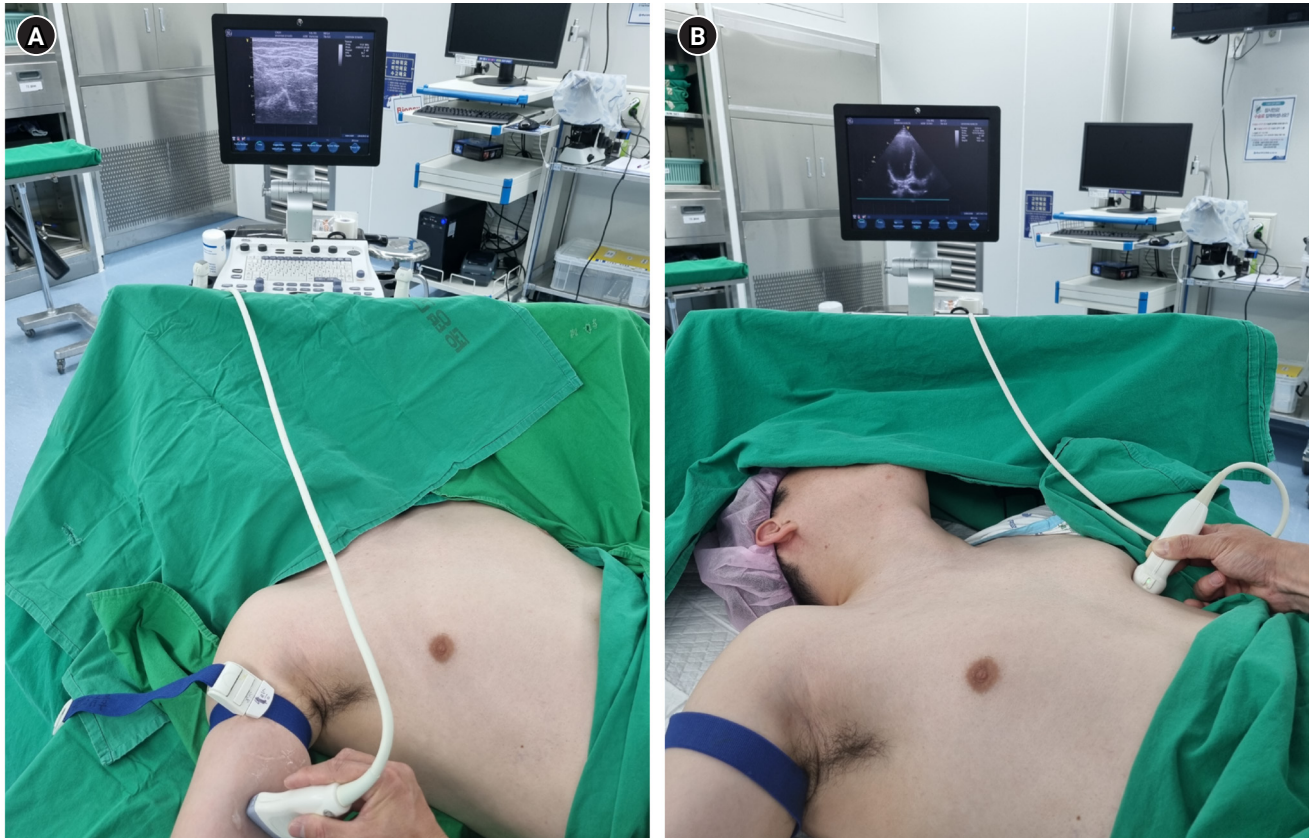
Figure 1. Before sterile draping: (A) rapid assessment of the peripheral vein by linear probe (12L) and (B) the best point for echocardiography in the apical four-chamber or subcostal view clearly shows the right atrial cavity by the echocardiographic probe (3Sc-RS) (GE Vivid S5 Ultrasound System).

ratio (LR) were calculated for TTE and CXR. Positive LR (LR+) was calculated as follows: sensitivity/(1–specificity). Negative LR (LR–) was calculated as follows: (1–sensitivity)/specificity.

RESULTS

We analyzed the records of 110 patients who underwent PICC placement at the Chungnam University Hospital between January 2022 and August 2023. Among these, 103 patients underwent the procedure directly on site without relocation. Seven patients who had previously undergone PICC placement (failed or removed once) were relocated to the operating room. Of the 110 patients who underwent PICC placement, eight were excluded from this study because the right atrial cavity could not be identified clearly on pre-procedural TTE. Two additional patients were excluded because one was not eligible for the predetermined RaPeVA and the other experienced puncture failure. Table 1 presents the basic characteristics of the remaining 100 patients and the materials used.

Among these patients, 92 experienced successful punctures in the first trial, while eight exhibited malpositioned catheters on periprocedural CXR and had to undergo the procedure in the other arm. Therefore, punctures were attempted a total of 108 times.

In the first trial, 90 patients were confirmed to have the catheter enter the right atrial cavity on TTE in real-time. Among these, 89 patients had the catheter tip located at the SVC–RA junction on post-procedural CXR (Figure 2); the remaining patient exhibited catheter malposition. However, 10 patients were not confirmed to have had the catheter advance toward the right atrial cavity on TTE. Of these, the PICCs were malpositioned in seven patients, and all were removed immediately.

A second trial was performed using the other arm in the eight patients with malpositioned catheters. In six of these patients, the catheters were confirmed to have entered the right atrial cavity on TTE in real-time, and all were properly positioned at the SVC–RA junction on the final CXR. The remaining two patients were not confirmed to have had the catheter

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Table 1. Enrolled patients and material characteristics

Variable	Total (n=100)	Catheter seen in RA (n=90)	Catheter not seen in RA (n=10)
Age (yr)	68±12	64±7	69±9
Sex (male:female)	48:52	–	–
BMI (kg/m^2)	25.3±12.4	26.3±9.3	18.21±8.6
Indications for PICC			
After cardiac surgery	32	28	4
After orthopedic surgery/rehabilitation	22	20	2
Chronic kidney disease	18	16	2
Cancer	11	10	1
Infectious disease	10	9	1
Gastrointestinal disease	7	7	0
Arrhythmia[a]	8	6	2
Atrial fibrillation	6	4	2
Ventricular junctional rhythm	2	2	0
Patients who underwent PICC placement previously (redo PICC placement)	7	4	3
Practice unit			
Intensive care unit	61	59	2
General ward and rehabilitation center	32	26	6
Operating room (for redo PICC placement)	7	5	2
PICC material[b]			
5-Fr double-lumen, arrow PICC	69	65	4
5-Fr triple-lumen pro-PICC	31	25	6

Values are presented as mean±standard deviation or number.

RA: right atrium; BMI: body mass index; PICC: peripherally inserted central catheter.

a) Arrhythmia refers to a rhythm measured using an electrocardiogram during the procedure; b) PICC materials were randomly assigned to the practitioner depending on product availability.
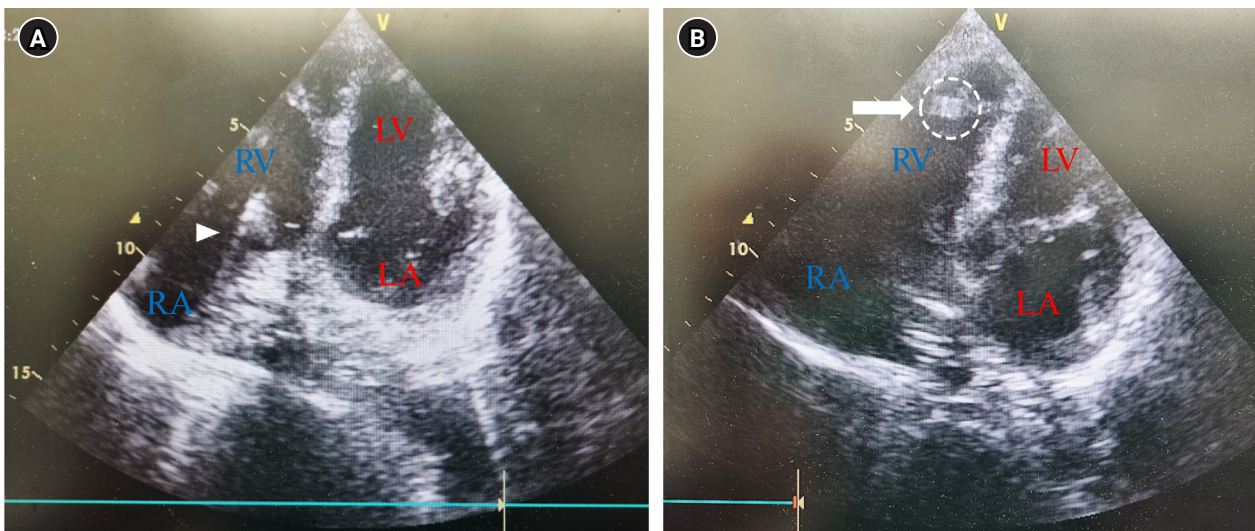
Figure 2. Transthoracic echocardiography during peripherally inserted central catheter, apical four-chamber view: (A) hyperechogenic line (arrowhead represents the catheter heading from the RA to the RV) and (B) hyperechogenic artifact (arrow represents the catheter tip at the RV). LV: left ventricle; RV: right ventricle; RA: right atrium; LA: left atrium.

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enter the right atrial cavity from the other arm, and the final CXR indicated malposition. Therefore, PICC placement was deemed to have failed, and the PICCs were removed immediately (Figure 3).

The outcomes of the diagnostic tests were calculated by predicting catheter placement for 108 procedures, combining the first and second trials. Catheter misplacement was detected using TTE with sensitivity, specificity, positive predictive value, and negative predictive value of 97% confidence interval (CI; 91.31%–99.36%), 90% CI (55.50%–99.75%), 99%, and 75%, respectively. The LR+ and LR– were 9.69 (95% CI, 1.5–62.3) and 0.03 (95% CI, 0.01–0.1), respectively (Table 2).

Patient data were collected based on the catheter position confirmed using CXR, present illness, history of arrhythmia,

patient age, and access location for complications associated with PICCs. Complications associated with PICCs that occurred within 1 month of the procedure were followed up after the procedure. In total, 68 of the 100 analyzed patients had their catheters removed because of treatment termination, self-removal, or death. Catheter-associated complications were communicated to the attending physicians after a formal consultation with all relevant departments.

Repositioning was indicated when the catheter tip did not reach the SVC–RA junction or pass through the right atrial cavity on post-procedural CXR. Four catheters required repositioning (all withdrawn), including three from the right basilic approach and one from the left brachial approach. In one of these four cases, the catheter passed through the tri-
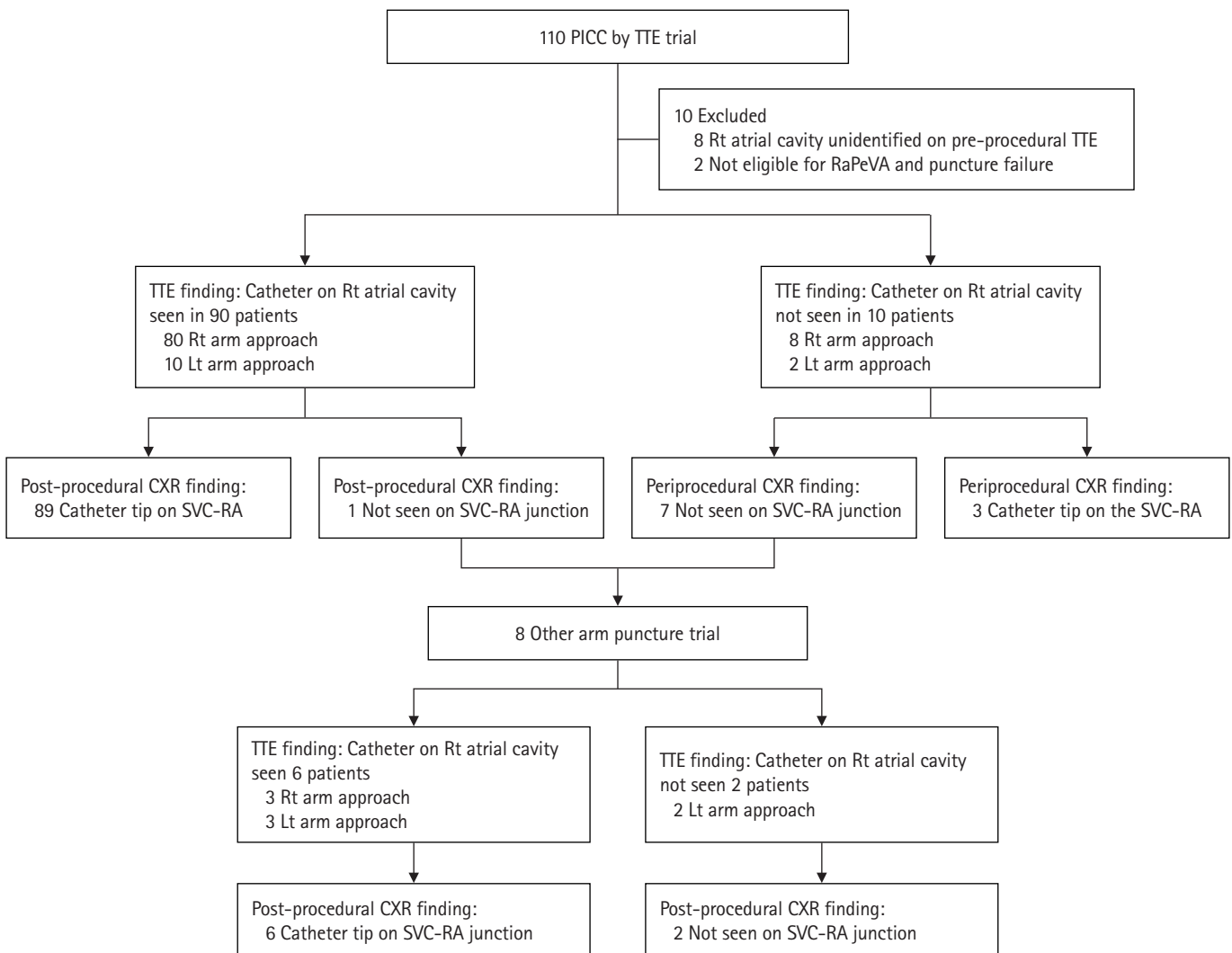
Figure 3. Study protocol used to analyze the diagnostic test. PICC: peripherally inserted central catheter; TTE: transthoracic echocardiography; RaPeVa: rapid peripheral vein assessment; Rt: right; Lt: left; CXR: chest x-ray; SVC–RA: superior vena cava–right atrium.

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Table 2. TTE as a diagnostic test for PICC detection

Diagnostic test	CXR findings		
	Positive	Negative	Total
TTE detection in the right atrial cavity			
Positive	95	1	96
Negative	3	9	12
Total	98	10	108

TTE: transthoracic echocardiography; PICC: peripherally inserted central catheter; CXR: chest x-ray.

Table 3. PICC placement results and complications

Variable	Value
PICC puncture trials, access route (times)	
First arm, first trial	100
Basilic vein, right	52
Brachial vein, right	36
Basilic vein, left	9
Brachial vein, left	3
Other arm, second trial	8
Basilic vein, right	3
Basilic vein, left	2
Brachial vein, left	3
Total trials (times)	108
Secondary endpoint (case)	
Optimizing catheter placement after post-procedural CXR	4
Withdrawal	4
Introducing forward	0
PICC failure	2
SVC syndrome	1
Subclavian vein stenosis and multiple collaterals	1
Complication	
Catheter-related infection	2
Catheter thrombosis	6

PICC: peripherally inserted center catheter; CXR: chest x-ray; SVC: superior vena cava.

cuspid valve, reached the right ventricle, and was withdrawn in real-time (Supplementary Video 1). Fluoroscopy or C-arm was not performed for catheter repositioning in any cases. Post-procedural CXR findings were the only reference for the length of catheter withdrawal. Two patients developed catheter-related infections, identified through blood culture analyses. Additionally, six patients experienced catheter thrombosis, which explained the ipsilateral arm edema and loss of PICC function in these cases. Of these six cases, five and one involved brachial and basilic approaches, respectively. All complicated PICCs were immediately removed (Table 3).

DISCUSSION

In this study, we employed a simple diagnostic method for catheter detection using TTE during PICC placement. Our method demonstrated sensitivity, specificity, positive predictive value, and negative predictive value of 97%, 90%, 99%, and 75%, respectively, indicating that the method is reliable. The LR+ was 9.69 and LR– was 0.03. Thus, we had strong evidence for ruling out catheter misplacement in most cases using this method.

PICC placement has been performed at our center by the Department of Cardiovascular and Thoracic Surgery since March 2020. Initially, the method described in this paper was only used for a portion of the patients admitted to the intensive care unit in our department. Gradually, its application expanded to include patients with high frailty who were difficult to move to other units. Previously, our center usually placed PICCs using C-arm in a vascular laboratory or operating room equipped with a fluoroscope. However, considerable effort and risk are involved when transferring critically ill patients to certain procedural units. Furnishing a unit with the equipment necessary for PICC procedures is more useful than relocating the patients to separate procedural units.

POCUS is extensively used in various ward and intensive care unit procedures. The cardiovascular surgeon who performed procedures (YCJ) in this study specializes in treating critically ill patients and is familiar with the percutaneous puncture technique, central catheter insertion, and chest and vascular anatomy, and can promptly and accurately detect artifacts in the heart using TTE. However, this method does not require advanced techniques or detailed interpretation during TTE. Instead, it simply identifies whether catheter artifacts are present in the right atrial cavity. Classical blind techniques (including CXR) are inferior to methods that use several different tools for detecting malposition [12]. Similar to C-arm and fluoroscopy, electrocardiography-electromagnetic guidance is an alternative to the existing methods [13]. However, electromagnetic guidance is not widely utilized in South Korea because of insurance coverage guidelines for PICC procedures.

In a retrospective study at a single institution, Kwon et al. [14] reported that optimal tip positions were achieved in the first trial in 91.6% of bedside PICC procedures. In 3.5% of the patients, a re-trial PICC placement or failure occurred. Even if multiple punctures are successfully tried in one arm, the

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arm can develop angioedema. Catheter malposition is dire for both practitioners and patients. In the present study, if basic or brachial vein access failed after a puncture in the first arm, an immediate trial was performed with the other arm rather than with the same arm. Deep or superficial thrombosis frequently occurs in the arm when one or more veins are used in patients with high frailty or severe comorbidities [15]. Among our patients, 18% had stage 1–4 chronic kidney disorders, with seven individuals undergoing dialysis with arteriovenous fistulae in their arms. In these patients, if thrombosis occurred while placing a catheter in an upper extremity vein or if injuries were caused by puncture failure, creating an arteriovenous fistula or accessing a dialysis vessel may be challenging in the future.

However, our method involved several difficulties. Performing the procedure at the bedside may be convenient for the patient, but greater preparation and maintenance are required to achieve readiness at the bedside compared to operating rooms, especially considering the necessity of applying sterile drapes for the arm, chest, and two probes. If patients have a sternotomy wound immediately after heart surgery, sterilizing the drape on the chest can be difficult. In this study, 29% of the patients underwent procedures in the intensive care unit immediately after heart surgery. However, the catheter-related infection complication rate (2%) was consistent with those reported in other studies [7,8,14,16].

One advantage of our method is that while fluoroscopy requires at least two practitioners, this technique usually requires only one practitioner, provided that the patient is cooperative. Importantly, the patients, practitioners, and assistants are not exposed to radiation during the procedure. Additionally, the procedural cost is less than that of fluoroscopy in South Korea.

Lack of familiarity with TTE may hinder identification of the echocardiographic window in the right atrial cavity, and fully identifying the SVC using TTE is challenging. Locating the SVC using transesophageal echocardiography is easy, but the procedure is invasive, causes discomfort to the patient, and requires considerable practice. In this study, pre-procedural TTE failed to visualize the right atrial cavity in seven patients who underwent postcardiac surgery and one patient with cachexia in the rehabilitation unit. Consequently, these eight patients were excluded from this study. The SVC–RA junction can be visualized through the modified apical five-chamber view, modified parasternal short-axis view, and modified subcostal view [17]. However, periprocedural TTE led to false-positive catheter detection in one patient in our study. This patient had

a body mass index of 12.43 kg/m^2, and the rib shaft was mistaken for a catheter in the TTE apical four-chamber view. POCUS has recently been used at the bedside. Owing to the ease of use of TTE, repetitive training will help practitioners find a good echocardiographic window by enabling simultaneous use of multiple modified views of the right atrial cavity and SVC–RA junction [6].

This study has some limitations. It was single-center and retrospective: numerous patients who underwent cardiovascular surgery and those with high frailty were included, and selection bias inevitably occurred. Therefore, applying our method to all patients requiring PICCs would be premature. This method is intended for catheter detection only and not for PICC placement itself. It is unrelated to the success rates of numerous PICC placement protocols and is not comparable. Moreover, a single cardiovascular surgeon familiar with ultrasound and echocardiography performed the entire procedure for every patient. The various ultrasonography devices used in this study were heterogeneous in performance and resolution. Skilled detection and placement have a learning curve. This method is not comparable with several other detection methods that use electromagnetic guidance or fluoroscopy. Nevertheless, this method could yield better PICC results when POCUS is used in many centers.

In conclusion, bedside TTE is a reliable tool for detecting catheter misplacement and optimizing catheter tip positioning during PICC placement. In the future, we plan to conduct a comparative study using various tools that require central venous access.

CONFLICT OF INTEREST

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

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Conceptualization: YCJ, MWK. Data curation: HSP. Formal analysis: MSS. Methodology: YCJ, HSP. Project administration: MWK. Visualization: MSS, HSP, YCJ. Writing–original draft: YCJ. Writing–review & editing: YCJ, MSS, MWK.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4266/acc.2024.00150.

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Comparison of ropivacaine, bupivacaine, and lignocaine in femoral nerve block to position fracture femur patients for central neuraxial blockade in Indian population

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Background: Patients with a fractured femur experience intense pain during positioning for neuraxial block for definitive surgery. Femoral nerve block (FNB) is therefore often given prior to positioning for analgesia. In our study, we compare the onset and quality of block of 0.25% bupivacaine, 0.5% ropivacaine, and 1.5% lignocaine for FNB in fracture femur patients.
Methods: Seventy-five adult femur fracture patients were equally and randomly divided into three groups to receive 15 ml of either 0.25% bupivacaine (group B), 0.5% ropivacaine (group R), or 1.5% lignocaine (group L) for FNB prior to positioning for neuraxial blockade. Onset and quality of block were assessed, as well as improvement in visual analog scale (VAS) score, ease of positioning, and patient satisfaction.
Results: Percentage decrease in VAS was found to be highest in group R (82.8%) followed by groups L and B. Time to achieve a VAS of less than 4 was found to be 26.2±2.4 minutes in group B, 8.5±1.9 minutes in group R, and 4.1±0.7 minutes in group L (P<0.001). In group B, 12 patients required additional fentanyl to achieve a VAS <4. Patient positioning was reported to be satisfactory in all patients in group R and L, while in B it was satisfactory in 13 (52%) patients only. Patient acceptance of FNB was 100% in group R and L, but only 64% in group B.
Conclusions: Based on our findings, 0.5% ropivacaine is a favorable choice for FNB due to early onset, ability to yield a good quality block, and good safety profile.

Key Words: anesthesia; block; bupivacaine; femoral; lignocaine; nerve block; orthopedic; ropivacaine

INTRODUCTION

One of the common causes of hospital admissions in the elderly is fractures resulting from falls, especially femoral neck fractures. There were an estimated 1.66 million hip fractures worldwide in 1990. According to the epidemiologic projections, this worldwide annual number will rise to 6.26 million by the year 2050 [1]. A study on hip fracture incidence performed in the Rohtak district of north India, the most populous country in the world, reported a crude incidence above the age of 50 years of 129 per 100,000 [2]. The corresponding figures were 105 and 159 per 100,000 men and women, respectively.

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The vast majority of femur fractures are treated by surgical repair, which is usually conducted under regional anesthesia. Central neuraxial blockade (CNB) is a widely accepted anesthetic technique for these cases [3]. However, positioning for CNB can be extremely painful for patients, resulting in sympathetic activation and a subsequent increase in cardiac work load that may compromise high risk cardiac patients. Effective management of pain is important for patient comfort and to facilitate the performance of the CNB. Pain management in femur fracture patients has traditionally been based on systemic opioids, which have multiple adverse effects in frail and elderly patients. Blockade of the femoral nerve has been proposed as an alternative [4-8]. Femoral nerve block (FNB) produces good analgesia with very few side effects compared to opioids and non-steroidal anti-inflammatory drugs.

Most studies have reported using lignocaine for FNB. Lignocaine is an intermediate acting local anesthetic (LA) agent. Bupivacaine provides a longer duration of action, but has potentially life-threatening cardiac toxicity. Ropivacaine has emerged as a new and safer alternative to bupivacaine. Ropivacaine has a greater degree of motor sensory differentiation, resulting in a relative reduction in motor blockade and less cardiac toxicity than bupivacaine [9]. Few studies, however, have directly compared the effectiveness of ropivacaine with other LAs in patients with femur fractures in terms of satisfactory analgesia and ease of positioning prior to CNB.

MATERIALS AND METHODS

This prospective, randomized interventional study was conducted in a tertiary care teaching institute (Vardhman Mahavir Medical College and Safdarjung Hospital) over a period of 1 year after approval from the Institutional Ethics Board (IEC/VMMC/SJH/Thesis/October/2017-029, dated 30.10.2017). Informed written consent was obtained.

All American Society of Anesthesiologists grade I and II patients between 18 and 75 years who were scheduled to undergo surgery for fracture neck femur and who consented to be a part of the study were included. Patients excluded from the study were those who had no baseline pain (visual analog scale [VAS] score <4), any contraindications to CNB, known allergy to LA agents, those requiring fixation of multiple fractures and therefore general anesthesia, those with pre-existing peripheral neuropathies, inflammation or infection over the femoral injection site, or those with impaired cognition or dementia making assessment of pain difficult.

After a detailed pre-anesthetic check-up, complete systemic examination and relevant investigations, the purpose and protocol of the study were explained to patients. Patients were told to rate their pain on a scale of 0–10 where 0 denoted no pain and 10 denoted the worst pain imaginable (VAS). No sedative premedications were prescribed. Upon arrival in the premedication room adjoining the operating room (OR), standard monitoring was performed, and an intravenous (IV) line was secured.

Patients were randomized into three groups by a computer-generated randomization algorithm. All patients received ultrasound guided FNB prior to transfer to the main operating theatre. The test drug in group B was 15 ml of 0.25% bupivacaine, while that in group R was 15 ml of 0.5% ropivacaine and in group L was 15 ml of 1.5% lignocaine. Drugs were prepared by a physician other than the one performing the block. Sensory blockade was evaluated at 5-minute intervals after performing the block using loss of perception to pinprick in the anterior and medial parts of the thigh (corresponding to femoral nerve sensory distribution).

Sensory block was graded as follows [10]. Grade 0 (block failure): sharp pin felt even after 30 minutes; grade 1: analgesia, dull sensation felt; grade 2: anesthesia, no sensation felt. After achieving sensory loss as evaluated by skin pinprick, the patient was moved to the OR where CNB was administered in a sitting position.

VAS scores were noted before the block, after achieving complete block, and during positioning for CNB. If a patient reported VAS score ≥4 during positioning, the procedure was stopped, and IV fentanyl 0.5 μg/kg was given every 5 minutes until the patient's pain score decreased to <4 or up to a maximum dose of 3 μg/kg (whichever came first). If a pain score <4

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could not be achieved, patients were excluded from the study. Positioning was reattempted after reduction of VAS to <4. VAS score during patient positioning and the quality of the position were recorded by the anesthesiologist administering the CNB. Duration of time to achieve VAS was recorded, as was the performance time (defined as the time from the beginning of patient positioning to the end of the performance of CNB). Patient positioning was evaluated as 0 (unsatisfactory) or 1 (satisfactory).

Intraoperative monitoring of relevant parameters such as heart rate, non-invasive blood pressure, and oxygen saturation was done. Any episode of hypotension (decrease in mean arterial pressure, mean arterial pressure more than 20% of the baseline value) or bradycardia (heart rate less than 60/min) were noted and managed. Following surgery, all patients were transferred to the postanesthetic care unit, where standard monitoring was performed. Patient experience with FNB was evaluated 24 hours later, in the orthopedics ward, using a two-point score: 0, bad, I will never repeat it; 1, good, if necessary, I would repeat it.

Statistical Analysis

Categorical variables are presented as numbers and percentages (%) and continuous variables are presented as means ±standard deviations and medians. Normality of data was tested by the Kolmogorov-Smirnov test. If normality was rejected, then non-parametric tests were used.

Statistical tests were applied as follows: (1) quantitative variables were compared using analysis of variance with repeated measurements/Kruskal Wallis tests (when data were not normally distributed) between three groups and paired t-test/ Wilcoxon ranked sum tests within the groups across follow-ups. (2) Qualitative variables were correlated using the chi-square test/Fisher's exact test. A P-value of <0.05 was considered statistically significant. Data were entered into excel spreadsheets and analyzed using IBM SPSS version 21.0 (IBM Corp.).

RESULTS

A total of 75 patients were included in the study: 25 each in groups B, R. and L (Figure 1). The demographic profile of the study population is described in detail in Table 1, along with group-wise distributions. There were no significant differences in patient characteristics among the three groups (P>0.05). Preoperative vital parameters are presented in Table 2; these were also comparable among the three test groups.

Patients were assessed preoperatively using VAS before FNB intervention and at the time of positioning patients for CNB after FNB. No case of block failure was observed in any test subject. Differences in VAS scores before and after FNB are presented in Table 3 for the three groups. Scores were comparable before FNB; however, after the intervention, statistically significant differences were found in VAS scores between groups (bupivacaine vs. ropivacaine and bupivacaine vs. lignocaine comparisons, but not the ropivacaine vs. lignocaine comparison). Percentage decrease in VAS was highest in group R (82.8%) followed by groups L (81.5%) and B (52.4%). Time to achieve a VAS less than 4 was 26.2±2.4 minutes in group B, 8.5±1.9 minutes in group R, and 4.1±0.7 minutes in group L. Differences among the three groups were statistically significant, as shown in Table 3.

Grade 1 sensory block was achieved in all patients in all groups. Grade 2 sensory block was achieved in all patients in groups R and L. In group B, it was achieved in only 13 patients (52%). There were statistically significant differences in groups B vs. R and B vs. L. Average time taken to achieve grade 1 sensory block was 11.7±1.8 minutes in group B, 3.9±0.5 minutes in group R, and 2.4±0.3 minutes in group L. Average time for grade 2 sensory block to set in was 26.2±2.4 minutes in group B, 8.7±1.5 minutes in group R, and 4.1±0.7 minutes in group L. These differences among groups were statistically significant (Table 3).
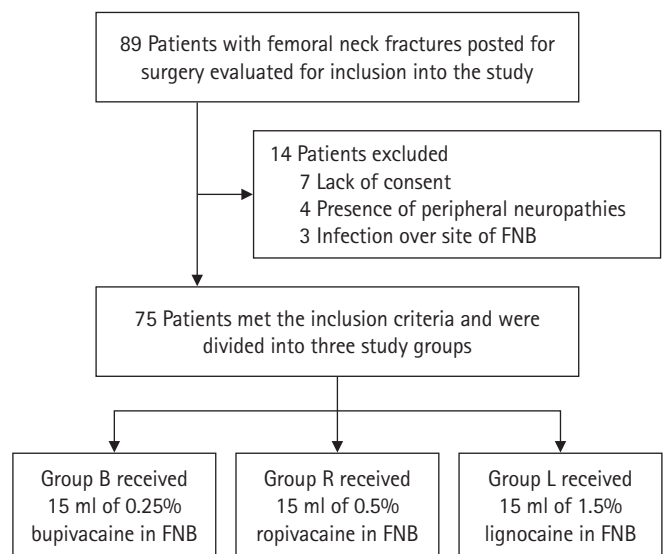
Figure 1. Flowchart for patients selection and division into study groups. FNB: femoral nerve block.

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Table 1. Demographic characteristics of the patient population with group-wise division

Variable	Group B (n=25)	Group R (n=25)	Group L (n=25)
Age (yr)			
Mean±SD	37±12	37±10	36±18
Median (min–max)	33 (26–71)	35 (21–60)	30 (16–73)
IQR	30–37	29–45	25–50
Sex			
Male	7 (28)	7 (28)	7 (28)
Female	18 (72)	18 (72)	18 (72)
Mean weight (kg)	60.2	62.2	56.4
ASA grading			
I	21 (84)	21 (84)	21 (84)
II	4 (16)	4 (16)	4 (16)
Type of fracture (%)			
Inter-trochanteric	12	20	20
Neck of femur	8	16	24
Shaft of femur	80	64	56

Values are presented as number (%) unless otherwise indicated.
Group B: patients given 15 ml of 0.25% bupivacaine in femoral nerve block (FNB); Group R: patients given 15 ml of 0.5% ropivacaine in FNB; Group L: patients given 15 ml of 1.5% lignocaine in FNB; SD: standard deviation; IQR: interquartile range; ASA: American Society of Anesthesiologists.

Table 2. Preoperative vitals parameters of the study population with group-wise division

Variable	Group B (n=25)	Group R (n=25)	Group L (n=25)	P-value
Heart rate (beats/min)				0.523
Mean±SD	87.6±10.5	84.7±11.6	84.6±10.0	
Median (min–max)	88 (76–126)	86 (69–120)	86 (66–110)	
IQR	79.8–90.0	76.0–94.0	76.8–89.3	
Mean arterial pressure (mm Hg)				0.361
Mean±SD	83.0±4.6	82.4±5.7	84. 6±5.8	
Median (min–max)	81 (78–92)	81 (75–91)	85 (76–98)	
IQR	80.0–84.0	77.8–88.3	78.6–89.0	
Respiratory rate (breaths/min)				0.307
Mean±SD	16.0±1.8	15.9±1.8	16.6±1.7	
Median (min–max)	16 (13–19)	15 (14–19)	16 (14–19)	
IQR	15.0–16.5	14.8–16.3	15.0–18.0	
Oxygen saturation (%)				1.000
Mean±SD	99.5±0.7	99.5±0.7	99.5±0.7	
Median (min–max)	100 (98–100)	100 (98–100)	100 (98–100)	
IQR	99–100	99–100	99–100	

Group B: 0.25% bupivacaine; Group R: 0.5% ropivacaine; Group L: 1.5% lignocaine; SD: standard deviation; IQR: interquartile range.

Regarding the requirement of fentanyl for positioning for CNB, there were statistically significant differences in groups B vs. R and B vs. L; 12 (48%) patients in group B required additional fentanyl, while no patients in groups R or L required fentanyl. Average time required to perform CNB was 9.9±1.3 minutes in group B, 8.8±0.8 minutes in group R, and 8.3±0.7 minutes in group L (Table 3). There were significant differenc-

es in groups B vs. R (P=0.002), B vs. L (P<0.001), and R vs. L (P=0.038). Patient positioning was satisfactory in all patients in groups R and L, while in group B it was satisfactory only in 13 patients. There were significant differences between groups B and R, as well as B and L. Patient acceptance of FNB was 100% in groups R and L, while in group B only 16 patients (64%) considered the experience to be good. This difference in accep-

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Table 3. Group-wise comparison of FNB onset, quality, improvement in VAS and time to perform neuraxial block

Variable	Group B (n=25)	Group R (n=25)	Group L (n=25)	P-value
VAS score before FNB				0.548
Mean±SD	7.9±0.9	7.72±0.84	7.68±0.95	B vs. R: 0.351
Median (min–max)	8 (6–9)	8 (6–9)	8 (6–9)	R vs. L: 0.902
IQR	7.8–8.3	7.0–8.0	7.0–8.0	L vs. B: 0.336
VAS score after FNB				<0.001
Mean±SD	3.7±1.2	1.3±0.5	1.4±0.5	B vs. R: <0.001
Median (min–max)	3 (2–7)	1 (1–2)	1 (1–2)	R vs. L: 0.560
IQR	3.0–4.3	1.0–2.0	1.0–2.0	L vs. B: <0.001
Time to achieve VAS <4 (min)				<0.001
Mean±SD	26.2±2.4	8.5±1.9	4.1±0.7	B vs. R: <0.001
Median (min–max)	27 (20–29)	9 (3–10)	4 (3–5)	R vs. L: <0.001
IQR	25–28	8–10	4.0–4.5	L vs. B: <0.001
Time to achieve grade 1 sensory block (min)				<0.001
Mean±SD	11.7±1.8	3.9±0.5	2.4±0.3	B vs. R: <0.001
Median (min–max)	12 (8–15)	4 (2–4.5)	2.5 (2–2.9)	R vs. L: <0.001
IQR	10.8–13	3.9–4	2.0–2.7	L vs. B: <0.001
Time to achieve grade 2 sensory block (min)				<0.001
Mean±SD	26.2±2.4	8.7±1.5	4.1±0.7	B vs. R: <0.001
Median (min–max)	27 (20–29)	9 (3–10)	4 (3–5)	R vs. L: <0.001
IQR	25–28	8–10	4–4.5	L vs. B: <0.001
Performance time for CNB (min)				<0.001
Mean±SD	9.9±1.3	8.8±0.8	8.3±0.7	B vs. R: 0.002
Median (min–max)	10 (8–13)	9 (8–11)	8 (7–9)	R vs. L: <0.001
IQR	9–11	8–9	8–9	L vs. B: 0.038

FNB: femoral nerve block; VAS: visual analog scale; Group B: 0.25% bupivacaine; Group R: 0.5% ropivacaine; Group L: 1.5% lignocaine; SD: standard deviation; IQR: interquartile range.

tance was statistically significant (B vs. R, P=0.002 and B vs. L, P=0.002). No vascular punctures occurred nor were there any indications of systemic toxicity such as seizures, arrhythmias, cardiovascular collapse, hypotension, or bradycardia among patients in our study.

DISCUSSION

Advancements in the field of healthcare have increased the average life expectancy worldwide. The incidence of hospital visits by geriatric patients with health problems such as fractures resulting from falls is increasing along with the increase in size world-wide of the geriatric population. Analgesia during positioning of femur fracture patients has traditionally relied on systemic opioids. Blockade of the femoral nerve was proposed as an alternative method of pain control in such situations to avoid the side effects of opioids as early as 1977 [6]. The benefits of femoral nerve blockade have been corroborated in multiple studies. Sia et al. [7] conducted a randomized study

in femur fracture patients undergoing surgery under neuraxial blockade. They compared the ease and comfort of positioning during spinal anesthesia of FNB versus IV fentanyl and concluded that FNB was more advantageous. Similarly, Jadon et al. [8] reported significantly better patient satisfaction and lower VAS scores when lignocaine-based FNB was given prior to positioning during spinal anesthesia in fracture femur patients as compared to IV fentanyl.

Many researchers have compared various LA agents in FNB performed for primary surgery. Fanelli et al. [11] conducted a double-blind study comparing 0.75% ropivacaine, 0.5% bupivacaine, and 2% mepivacaine for sciatic and femoral block for elective hallux valgus repair. The authors concluded that 0.75% ropivacaine was the most suitable choice of LA, with an onset similar to that of mepivacaine and postoperative analgesia intermediate between bupivacaine and mepivacaine. Similar to our study findings, the onset of sensory and motor blockade with ropivacaine was significantly shorter than with bupivacaine. However, the duration of postoperative analgesia was

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longer with both bupivacaine and ropivacaine, which may be due to both sciatic and femoral block in their study versus FNB only in our study, as well as the nature of the surgery. Similar findings were reported in a multicenter study conducted by the Italian Society of Anesthesia [12] of patients undergoing foot and ankle surgery under sciatic-femoral block with increasing doses of ropivacaine (0.5%, 0.75%, and 1%) and 2% mepivacaine. The authors concluded that 0.75% ropivacaine was the most suitable choice of LA for sciatic-femoral block, with an onset similar to mepivacaine and prolonged postoperative analgesia.

Kuthiala and Chaudhary [13] published a review article in which they reported that ropivacaine was a well-tolerated regional anesthetic agent, effective for surgical anesthesia as well as the relief of postoperative and labor pain. The efficacy of ropivacaine was similar to that of bupivacaine and levobupivacaine for peripheral nerve blocks. Clinically adequate doses of ropivacaine appear to be associated with a lower incidence or grade of motor block than bupivacaine. Thus, ropivacaine, with its efficacy, lower propensity for motor block, and reduced potential for CNS toxicity and cardiotoxicity, appears to be a favorable option for regional anesthesia and management of postoperative pain.

The power of our study lies in its novelty. There is a paucity of literature comparing different LA agents in FNB given prior to positioning for CNB of painful fractures. Previous studies [11,12] have compared LA agents for lower limb blocks performed for surgical procedures. Second, our outcome measures included objective criteria such as VAS score and time to performance of block, as well as subjective criteria such as patient feedback. This allowed for comprehensive comparison of LAs as described above. There are certain limitations to our study that should be taken into consideration. The sample size was small due to the limited duration of the study. The anesthesiologist performing the FNB could not be kept constant due to staffing reasons and rotational postings. Studies with different concentrations of each drug need to be conducted to determine the ideal concentration for sensory blockade.

Based on our findings, we conclude that FNB with 0.5% ropivacaine before positioning for CNB provides good pain management and facilitates performance of CNB with excellent patient acceptance, hence improving overall quality and efficiency of care. Ropivacaine exhibits a faster onset of action than bupivacaine and a longer duration of action than both lignocaine and bupivacaine, with a better safety profile than bupivacaine.

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The efficacy of therapeutic hypothermia in patients with poor-grade aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis

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Background: This study evaluates the effectiveness of Therapeutic Hypothermia (TH) in treating poor-grade aneurysmal subarachnoid hemorrhage (SAH), focusing on functional outcomes, mortality, and complications such as vasospasm, delayed cerebral ischemia (DCI), and hydrocephalus.
Methods: Adhering to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines, a comprehensive literature search was conducted across multiple databases, including Medline, Embase, and Cochrane Central, up to November 2023. Nine studies involving 368 patients were selected based on eligibility criteria focusing on TH in poor-grade SAH patients. Data extraction, bias assessment, and evidence certainty were systematically performed.
Results: The primary analysis of unfavorable outcomes in 271 participants showed no significant difference between the TH and standard care groups (risk ratio [RR], 0.87). However, a significant reduction in vasospasm was observed in the TH group (RR, 0.63) among 174 participants. No significant differences were found in DCI, hydrocephalus, and mortality rates in the respective participant groups.
Conclusions: TH did not significantly improve primary unfavorable outcomes in poor-grade SAH patients. However, the reduction in vasospasm rates indicates potential specific benefits. The absence of significant findings in other secondary outcomes and mortality highlights the need for further research to better understand TH's role in treating this patient population.

Key Words: hypothermia; intracranial vasospasm; mortality; stroke; subarachnoid hemorrhage

INTRODUCTION

Therapeutic hypothermia (TH) has emerged as a critical intervention in the aftermath of cardiac arrest resuscitation, celebrated for its neuroprotective properties [1]. A key aspect of TH is its ability to effectively reduce cellular metabolism, leading to decreased oxygen and energy demands in brain cells [2,3]. This metabolic reduction plays an integral role in lowering in-

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tracranial pressure (ICP) and minimizing brain edema, which may help mitigate further brain injury [4,5].

Originally employed for its neuroprotective effects, the application of TH has since expanded to include various forms of acute brain injuries, especially those characterized by hypoxic-reperfusion injuries such as cerebral infarction, intracranial hemorrhage (ICH) traumatic brain injury (TBI), and subarachnoid hemorrhage (SAH) [6-9]. Despite its expanded use, the efficacy of TH in these scenarios, particularly in SAH, has sparked considerable debate [10]. Clinical studies have often yielded mixed or inconclusive results, highlighting a gap in the comprehensive understanding of TH's role in these contexts.

Of particular interest is the application of TH in poor-grade SAH, where patients are confronted with exacerbated challenges like heightened ICP and significant cerebral swelling. The management of such cases remains a complex and pressing issue in neurocritical care. This study aims to scrutinize and quantify the clinical outcomes of TH in the management of poor-grade SAH. By delving into the nuances of TH's application in this specific patient population, we hope to shed light on its potential benefits and limitations. This systematic review and meta-analysis aspire to provide a more detailed understanding of TH's therapeutic role in improving clinical outcomes for patients with poor-grade SAH, thereby contributing valuable insights to the field of neurocritical care.

MATERIALS AND METHODS

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement. The review was registered with the PROSPERO International prospective register of systematic reviews (registration number CRD42023479143).

Search Strategy and Data Extraction
Two independent reviewers systematically searched three databases (Medline, Embase, and the Cochrane Central Register of Controlled Trials). The search spanned from the inception of each database to November 2023, with no language or time restrictions. Search terms for each database can be found in Supplementary Table 1.

Using predefined criteria, two authors independently assessed all retrieved citations. Initially, titles and abstracts of identified articles were reviewed, excluding publications that clearly did not meet the inclusion criteria or were duplicative. Subsequently, two authors meticulously examined the full-

> **KEY MESSAGES**
>
> - Therapeutic hypothermia (TH) shows promise as a potential treatment for patients with poor-grade aneurysmal subarachnoid hemorrhage (SAH), suggesting a beneficial effect on clinical outcomes.
> - Despite some variability in study results, the systematic review and meta-analysis provide evidence supporting the efficacy of TH in improving neurological outcomes and reducing mortality rates among this patient population.
> - Further research is warranted to refine protocols, optimize timing, and identify the subset of SAH patients who would benefit most from TH, potentially shaping future clinical guidelines and treatment strategies.

texts of articles that appeared to align with inclusion criteria, with the aim of further assessing their potential relevance. Additionally, references within selected articles were scrutinized to identify relevant research. We conducted comprehensive analysis by including both randomized controlled trials (RCTs) and non-randomized studies (NRS), such as cross-sectional, case-control, and cohort studies.

All citations were downloaded and managed in Endnote X9 (Thompson ISI Research Soft), adhering to predefined standards. Rigorous checks were conducted to ensure data accuracy and completeness. Any discrepancies in search strategies or literature selection were resolved through discussion or arbitration led by experienced authors to maintain consistency.

Eligibility Criteria
All studies included in our meta-analysis adhered to the following criteria: (1) adult patients (aged 18 or older) diagnosed with SAH resulting from aneurysm rupture, confirmed by definitive imaging and clinical manifestations. (2) Poor-grade aneurysmal SAH (aSAH) patients (Hunt & Hess Scale 4, 5, and modified Fisher Scale 3, 4) who have undergone securing of the aneurysm through clipping or coiling. (3) Patients treated with TH (temperature maintained at 35 °C or less). (4) The control group received equivalent therapeutic approaches, excluding TH. (5) Studies providing comprehensive documentation of the therapeutic procedure, target temperature, and specified endpoints.

Exclusion criteria for clinical studies were: (1) no control group was established in the study. (2) Studies applying TH to patients with TBI, ICH, ischemic stroke, or hypoxic ischemic

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encephalopathy due to cardiac arrest, unrelated to SAH. (3) When TH is applied only during intraoperative procedures. (4) Studies involving animal models.

Assessing Risk of Bias and Certainty of the Evidence

To evaluate the risk of bias in the literature, two independent reviewers employed the bias risk assessment. When identifying RCTs, the revised Cochrane Risk of Bias 2 tool (RoB 2) was employed [11]. The RoB 2 evaluation covered several domains: randomization process, intervention deviations, outcome measurement, missing data, selective reporting, and an overall risk assessment. Each domain received judgments of "low risk," "some concerns," or "high risk" based on the evaluation criteria. The assessment of bias in NRS was conducted using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool, with necessary modifications made for suitability [12]. Any discrepancies were resolved through discussion or by involving a third reviewer until a consensus was achieved. The assessment of the certainty of evidence was conducted using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach, ensuring a rigorous and transparent evaluation of the evidence's quality.

Outcome Measurement

Baseline clinical data extracted comprised patient age, sex, target temperature of TH group, duration of TH, cooling method, Fisher grade, Hunt and Hess grade, treatment method of ruptured aneurysm. The primary outcome measures the effectiveness of TH in enhancing the clinical outcomes of aSAH patients, as assessed by the Glasgow Outcome Scale (GOS) or modified Rankin Scale (mRS) scores. An unfavorable functional outcome is defined as severe disability, indicated by a GOS prognosis scale score ≤3 or an mRS score of ≥4. Secondary outcomes include the evaluation of vasospasm (angiographic vasospasm was confirmed by diagnostic subtraction angiography, computed tomography (CT) angiography and perfusion scanning as well as by magnetic resonance imaging, with additional evidence of vasospasm observed in transcranial Doppler examinations), delayed cerebral ischemia (DCI; subsequent native CT imaging and required a newly demarcated cerebral infarction), the occurrence of hydrocephalus (in cases where ventriculo-peritoneal shunt was performed due to delayed hydrocephalus), and in-hospital mortality,

Statistical Analysis

For our meta-analysis, Stata 18 (Stata Corp.) was utilized as the primary statistical software. Our analysis focused on binary data, and we compiled the effect size from each dataset, presenting the cumulative effect as a risk ratio (RR) with a 95% confidence interval (CI). We considered a two-tailed P-value of less than 0.05 as statistically significant.

To evaluate study heterogeneity, we employed the I^2 statistic. An I^2 value over 30% indicated moderate heterogeneity, while values surpassing 50% and 75% signified substantial and considerable heterogeneity, respectively. In instances of notable heterogeneity (P<0.05, I^2>50%), an initial investigation into potential sources was conducted, followed by additional sensitivity analyses to ascertain the appropriateness of a random-effects model for our data synthesis. Notably, in this meta-analysis, each of the nine studies focused on patients with aSAH, though there were differences in their demographic characteristics and intervention protocols. Consequently, these variations necessitated the use of a random-effects model for the analysis. This approach was consistent with the heterogeneity observed in some of the analyses (where I^2>50%), as these variations could potentially lead to significant differences in study outcomes, thus underscoring the relevance of the random-effects model for data amalgamation. Additionally, the possibility of publication bias was assessed using a funnel plot. Sensitivity analyses were also performed using Stata 18 to pinpoint and address any individual studies that might have disproportionately influenced the overall analysis.

RESULTS

Study Selection

The search process and study exclusions are detailed in Figure 1. Initially, a comprehensive search yielded 3,174 studies, removing 561 duplicates. From the remaining 2613, 2548 were deemed irrelevant based on title and abstract screening. Full-text analysis was performed on 65 studies, resulting in the exclusion of 56 due to various reasons, including insufficient data, lack of a comparison group, and the amalgamation of different stroke types (Supplementary Table 2). Eventually, the remaining 9 studies with a total of 368 patients were included in our final analysis.

Characteristics of the Trials

This meta-analysis scrutinizes nine studies conducted between 1997 and 2018, encompassing a total of 368 participants,

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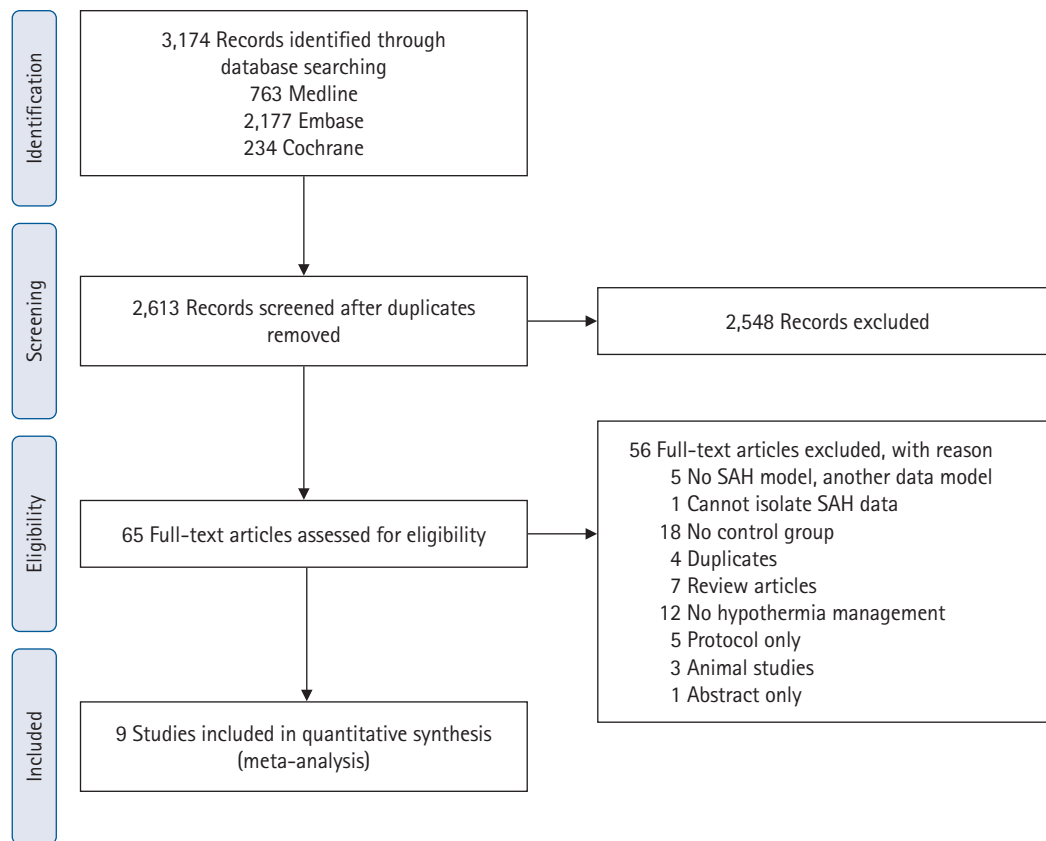
Figure 1. The flow diagram of the literature search. SAH: subarachnoid hemorrhage.

wherein 166 received TH and 202 served as controls. The study types comprised two RCTs and seven NRS, consisting of five retrospective observation studies, one prospective clinical pilot study, and one prospective matching study. In the analysis of nine reviewed studies, the overall risk of bias was assessed. Among the two RCTs, one exhibited a low risk of bias, while the other displayed a high risk of bias. Among the seven NRS, excluding one with moderate risk of bias, the remaining six indicated a serious risk of bias (Supplementary Fig. 1). Sample sizes ranged from 15 to 72 patients, with a diverse geographical distribution: five studies from Asia, three from Europe, and one from the USA. The overview was described in Table 1 [13-21].

The female ratio across these studies ranged from 27.4% to 80.0%, with a mean age range of 44.6 to 57.6 years. The presenting conditions primarily involved patients categorized under Hunt & Hess Scale 4, 5, modified Fisher Scale 3, 4, and World Federation of Neurosurgical Societies (WFNS) scale 4, 5. In the context of securing aSAH, five studies documented the use of either a surgical clip or coiling, two studies exclusively

involved coiling, and two did not specify the treatment method. Outcome measurements were gauged using the GOS and the mRS, with mean follow-up times spanning from 2 weeks to 1 year. Therapeutic interventions targeted temperatures between 33 °C to 35 °C, with induction times varying from 1 hour to 12 hours. Hypothermia was maintained for periods between 48 hours to 7 days, averaging 4.3 days, with rewarming rates employing passive warming or escalating at rates from 0.5 °C per day to 1 °C per 4 hours. Cooling methods encompassed 5 surface cooling, 2 endovascular cooling, and 2 mixed approaches. The interval from onset to cooling ranged from 2 hours to 48 hours, with shivering control systems implemented in 5 studies and absent in 4 studies. The summary of the main values in TH is detailed in Table 2.

Summary of Findings

In a comprehensive analysis comparing the hypothermia group to the standard care group, various outcomes were evaluated (Table 3). The risk of an unfavorable function outcome is anticipated at 740 per 1,000 individuals in the standard care

Table 1. Main characteristics of the included studies

Study	Study design	Study duration	Country	Female ratio (%)	Mean age (yr)	Presenting condition	Outcome measurement	Mean follow-up time
Muroi et al. (2008) [13]	Prospective clinical pilot study	NA	Switzerland	80.0	51.5	Fisher Scale 3, 4	GOS ≤3	1 yr
Neuman et al. (2008) [14]	Retrospective observation study	2002–2005	Czech Republic	62.2	52	Hunt & Hess Scale 4, 5	GOS >3	6 mo
Anei et al. (2010) [15]	Retrospective observation study	1997–2001	Japan	71.4	57.6	Fisher Scale 3, 4	mRS >3	3 mo or transfer day
Karnatovskaia et al. (2014) [16]	Retrospective observation study	2007–2012	USA	48.6	51.3	Fisher Scale 3, 4	mean mRS	1–6 mo
Kuramatsu et al. (2015) [17]	Prospective matching study	2010–2012	Germany	66.7	50.5	Hunt & Hess Scale 4, 5, modified Fisher Scale 3, 4, and WFNS scale 4–5	mRS >3	6 mo
Choi et al. (2017) [18]	Random clinical trial	2015–2016	Republic of Korea	59.1	52.9	Hunt & Hess Scale 4, 5 and modified Fisher Scale 3, 4	mRS >3	3 mo
Shui et al. (2018) [19]	Random clinical trial	2014–2016	China	27.4	44.6	modified Fisher Scale 3, 4	Vasospasm	2 wk
Rhim et al. (2022) [20]	Retrospective observation study	2015–2018	Republic of Korea	61.1	56.9	Hunt & Hess Scale 4, 5, modified Fisher Scale 3, 4, and WFNS scale 4–5	mRS >3	At discharge
Won et al. (2022) [21]	Retrospective observation study	2015–2018	Replic of Korea	61.1	57.5	Hunt & Hess Scale 5 and WFNS scale 5 (GCS <7)	mRS >3	At discharge & 3 mo

NA: not available; GOS: Glasgow Coma Scale; mRS: Modified Rankin Scale; WFNS: World Federation of Neurosurgical Societies; GCS: Glasgow Coma Scale.

Table 2. Summary of the main values in therapeutic hypothermia

Study	Total number	Intervention	Control	Aneurysm secured method	Target temperature (°C)	Induction time	Hypothermia time	Rewarming rate	Hypothermia method	Interval from onset to cooling	Shivering control system
Muroi et al. (2008) [13]	15	7	8	NA	33	NA	NA	NA	Endovascular cooling	NA	Yes
Neuman et al. (2008) [14]	37	25	12	Coil	34	<3 hr	>72 hr	Passive warming	Surface cooling	Mixed (immediately or after admission 4–5 days)	No
Anei et al. (2010) [15]	35	19	16	Clip or coil	34	NA	48 hr	1 °C/day	Surface cooling	<24	No
Karnatovskaia et al. (2014) [16]	35	19	16	Clip or coil	32–34	NA	>48 hr	<0.5 °C/hr	Surface cooling	NA	No
Kuramatsu et al. (2015) [17]	36	12	24	Clip or coil	35	NA	7±1 day	0.5 °C/day	Endovascular cooling	<48	Yes
Choi et al. (2017) [18]	22	11	11	Clip or coil	34.5	<1 hr	48	1 °C/day	Endovascular or surface cooling	<12	Yes
Shui et al. (2018) [19]	62	30	32	NA	35	4–12 hr	5–7 day	1 °C/hr	Surface cooling	2–8 hr	No
Rhim et al. (2022) [20]	54	18	36	Coil	34–35	NA	5 day	0.5 °C/day	Surface cooling	<8	Yes
Won et al. (2022) [21]	72	25	47	Clip or coil	34.5	<1 hr	48 hr	1 °C/day	Endovascular or surface cooling	NA	Yes

NA: not available.

Table 3. Summary of findings table using the GRADE methodology for outcomes comparing therapeutic hypothermia to standard care in poor grade subarachnoid hemorrhage

Outcome	Anticipated absolute effects[a] (95% CI)		RR (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with standard care	Risk with therapeutic hypothermia			
Unfavorable function outcome	740 Per 1,000	644 Per 1,000 (496–836)	0.87 (0.67–1.13)	271 (7 Studies)	⊕◯◯◯ Very low
Vasospasm	466 Per 1,000	294 Per 1,000 (191–447)	0.63 (0.41–0.96)	174 (4 Studies)	⊕◯◯◯ Very low
Delayed cerebral ischemia	451 Per 1,000	370 Per 1,000 (212–654)	0.82 (0.47–1.45)	130 (3 Studies)	⊕◯◯◯ Very low
Hydrocephalus	293 Per 1,000	334 Per 1,000 (184–609)	1.14 (0.63–2.08)	130 (3 Studies)	⊕◯◯◯ Very low
Mortality	336 Per 1,000	249 Per 1,000 (118–524)	0.74 (0.35–1.56)	219 (5 Studies)	⊕◯◯◯ Very low

GRADE: Grading of Recommendations Assessment, Development and Evaluation; CI: confidence interval; RR: risk ratio (relative effect).
a) The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

group, but it is reduced to 644 per 1,000 in the hypothermia group, indicating a potential benefit of TH. The RR for this outcome is 0.87 (95% CI, 0.67–1.13), suggesting a slight reduction in the risk of unfavorable outcomes, based on an analysis of 271 participants across seven studies. For vasospasm, the risk in the standard care group is 466 per 1,000, decreasing to 294 per 1,000 in the hypothermia group. The RR for vasospasm with TH is 0.63 (95% CI, 0.41–0.96), indicating a more pronounced effect in reducing the risk of vasospasm. This is derived from data involving 174 participants in four studies. Regarding DCI, under TH, the RR is 0.82 (95% CI, 0.47–1.45), indicating a slight reduction in risk, based on data from 130 participants across three studies. In the comparison of hydrocephalus incidence, the RR for the hypothermia group is 1.14 (95% CI, 0.63–2.08), suggesting a potential increase in risk. This assessment comes from 130 participants in three studies. Lastly, for mortality, the RR in the hypothermia group is 0.74 (95% CI, 0.35–1.56), suggesting a potential reduction in mortality risk. This result is based on data from 219 participants across five studies.

The overall level of certainty for these outcomes is very low. This indicates that further research could significantly impact our confidence in these estimates and potentially alter the current understanding of the effects of TH in these areas.

Functional Outcome

In a comprehensive review involving seven studies, a total of 271 participants were analyzed, with 117 in the intervention group and 154 in the control group. The focus was on comparing unfavorable outcomes between the TH group (intervention) and the standard group (control). However, the results revealed no significant difference in outcomes between these two groups. The RR was calculated as 0.87, with a CI ranging from 0.67 to 1.13 (Figure 2). The heterogeneity of the studies, as indicated by an I^2 value of 58.0%, suggests moderate variability among study results. The statistical significance was not reached (P=0.28), indicating that the difference in outcomes between the hypothermia and standard groups was not substantial. A funnel plot analysis was conducted to assess publication bias in the study, showing no significant discrepancies between the groups (Supplementary Fig. 2). Additionally, the results of the Egger's test, with a beta1 value of –1.06 and a P-value of 0.07, further indicate an absence of significant publication bias. These findings collectively support the conclusion of no significant differences in outcomes.

Secondary Outcomes

For vasospasm, which was evaluated across four studies involving 174 participants (71 in the intervention group and 103 in the control group), the RR was 0.63, with a CI of 0.41 to 0.96, and an I^2 of 0%, suggesting homogeneous study outcomes (Figure 3). The statistical significance of these findings was marked by a P-value of 0.03. In the case of DCI, examined in three studies with a total of 130 participants (48 in the intervention group and 82 in the control group), the RR was 0.82 with a CI of 0.47 to 1.45 (Figure 3). Despite the moderate het-

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Unfavorable functional outcomes

Study	Hypothermia Events	No	Control Events	No	Risk ratio with 95% CI	Weight (%)
Muroi 2008	4	3	4	4	1.14 [0.44, 2.94]	6.27
Neuman 2008	8	17	3	9	1.28 [0.41, 3.98]	4.60
Anei 2010	18	1	14	2	1.08 [0.87, 1.34]	28.17
Kuramatsu 2015	4	8	15	9	0.53 [0.23, 1.26]	7.32
Choi 2017	5	6	10	1	0.50 [0.25, 0.98]	10.49
Rhim 2022	7	11	25	11	0.56 [0.30, 1.04]	11.79
Won 2022	23	2	43	4	1.01 [0.87, 1.16]	31.34
Overall					0.87 [0.67, 1.13]	

Heterogeneity: $\tau^2 = 0.05$, $I^2 = 58.00\%$, $H^2 = 2.38$
Test of $\theta = 0$: z = -1.07, p = 0.28

Figure 2. Forest plot of studies comparing unfavorable functional outcomes in the therapeutic hypothermia group with that in the control group. The horizontal bars represent 95% confidence intervals (CIs).

erogeneity among the studies (I^2=39.4%), the results did not reach statistical significance (P=0.50). Regarding hydrocephalus, analyzed in three studies comprising 130 participants (48 in the intervention group and 82 in the control group), the RR stood at 1.14, with a CI of 0.63 to 2.08 and an I^2 of 3.5%, indicating low variability in the study results (Figure 3). However, these findings were not statistically significant (P=0.66).

Finally, for mortality, assessed across five studies including 219 participants (85 in the intervention group and 134 in the control group), the RR was 0.74 with a CI of 0.35 to 1.56 (Figure 3). With an I^2 of 49.0%, indicating moderate heterogeneity, the results showed no significant difference in mortality rates between the groups (P=0.42). These secondary outcome analyses provide a nuanced understanding of the intervention's effects, with only vasospasm demonstrating a significant difference.

Sensitive Analysis

In our comprehensive systematic review and meta-analysis, we evaluated the effectiveness of TH and conducted a sensitivity analysis to determine the influence of different study criteria on TH's functional outcomes (Supplementary Table 3). The analysis encompassed three distinct categories: Firstly, we considered six NRS, deliberately excluding one RCT, which involved a total of 249 patients. The observed risk ratio in this group was 1.00, suggesting that these studies did not significantly deviate from the overall analysis in terms of TH's impact on functional outcomes. Secondly, our focus shifted to more

recent research, specifically studies conducted after 2010, comprising 184 patients. Although the risk ratio of 0.69 in this category indicated a potential improvement in outcomes with TH, the CI, ranging from 0.46 to 1.05, did not support statistical significance, as it crossed the threshold of no effect. Lastly, we analyzed five studies that involved the introduction of a shivering control system, covering 199 patients. In this case, the risk ratio stood at 0.75, hinting at possible beneficial outcomes. However, similar to the previous category, the CI (0.52–1.07) was not conclusive enough to firmly establish these results. This sensitivity analysis helped in understanding the consistency and robustness of the observed effects of TH on functional outcomes across various study types and time frames.

DISCUSSION

TH has demonstrated neuroprotective functions in patients who remain unconscious post-cardiac arrest with return of spontaneous circulation [1]. Its effectiveness in reducing secondary brain injury mechanisms like cell edema and inflammation, thereby lowering ICP and brain damage is well documented [4,5]. By reducing body temperature, TH lessens cerebral oxygen demand and metabolism, significantly diminishing secondary brain injury, even under hypoxic conditions [2]. Additionally, its benefits extend to decreasing adenosine triphosphate consumption, inflammation, and seizure incidence, as well as stabilizing the blood-brain barrier, cumula-

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A Vasospasm

Study	Hypothermia Events	No	Control Events	No	Risk ratio with 95% CI	Weight (%)
Kuramatsu 2015	6	6	16	8	0.75 [0.40, 1.41]	45.34
Choi 2017	2	9	4	7	0.50 [0.11, 2.19]	8.31
Shui 2018	3	27	11	21	0.29 [0.09, 0.94]	13.13
Rhim 2022	6	12	17	19	0.71 [0.34, 1.48]	33.22
Overall					0.63 [0.41, 0.96]	

Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$
Test of $\theta = 0$: $z = -2.14$, $p = 0.03$

(axis: 1/8 1/4 1/2 1 2)

B Delayed cerebral ischemia

Study	Hypothermia Events	No	Control Events	No	Risk ratio with 95% CI	Weight (%)
Kuramatsu 2015	6	6	21	3	0.57 [0.32, 1.03]	44.28
Choi 2017	4	7	5	6	0.80 [0.29, 2.21]	22.79
Won 2022	8	17	11	36	1.37 [0.63, 2.96]	32.93
Overall					0.82 [0.47, 1.45]	

Heterogeneity: $\tau^2 = 0.10$, $I^2 = 39.36\%$, $H^2 = 1.65$
Test of $\theta = 0$: $z = -0.67$, $p = 0.50$

(axis: 1/2 1 2)

C Hydrocephalus

Study	Hypothermia Events	No	Control Events	No	Risk ratio with 95% CI	Weight (%)
Kuramatsu 2015	1	12	8	24	0.31 [0.04, 2.22]	9.08
Choi 2017	2	9	2	9	1.00 [0.17, 5.89]	11.24
Won 2022	11	14	14	29	1.35 [0.73, 2.50]	79.68
Overall					1.14 [0.63, 2.08]	

Heterogeneity: $\tau^2 = 0.02$, $I^2 = 3.50\%$, $H^2 = 1.04$
Test of $\theta = 0$: $z = 0.43$, $p = 0.66$

(axis: 1/16 1/4 1 4)

D Mortality

Study	Hypothermia Events	No	Control Events	No	Risk ratio with 95% CI	Weight (%)
Karnatovskaia 2014	11	8	5	11	1.85 [0.81, 4.21]	28.79
Kuramatsu 2015	2	10	4	20	1.00 [0.21, 4.71]	15.30
Choi 2017	0	11	4	7	0.11 [0.01, 1.85]	6.14
Rhim 2022	3	15	10	26	0.60 [0.19, 1.91]	21.45
Won 2022	5	20	22	25	0.43 [0.18, 0.99]	28.32
Overall					0.74 [0.35, 1.56]	

Heterogeneity: $\tau^2 = 0.33$, $I^2 = 49.02\%$, $H^2 = 1.96$
Test of $\theta = 0$: $z = -0.80$, $p = 0.42$

(axis: 1/128 1/16 1/2 4)

Figure 3. Forest plot of studies comparing the subarachnoid hemorrhage related complication and mortality in the therapeutic hypothermia group with that in the control group. (A) Fours studies reported vasospasm. The meta-analysis of risk ratio reported a statistically lower incidence of vasospasm in patients treated with therapeutic hypothermia. (B) Three studies reported delayed cerebral ischemia. There was no significant effect involving therapeutic hypothermia and delayed cerebral ischemia. (C) Three studies reported hydrocephalus. There was no significant effect involving therapeutic hypothermia and hydrocephalus. (D) Fives studies reported mortality. There was no significant effect involving therapeutic hypothermia and mortality. CI: confidence interval.

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tively improving outcomes in neurocritical patients [3].

Despite these foundations, TH's application in TBI and stroke has failed to consistently demonstrate significant efficacy [22-25], except in some cases of ischemic stroke [26]. Nonetheless, it is commonly used as a last resort in treating poor grade SAH, although systematic evidence supporting this practice is lacking. Our systematic review was conducted in light of this gap. While we found that TH does not significantly improve functional outcomes or mortality in SAH, it may reduce the incidence of vasospasm. This finding aligns with previous literature, suggesting a specific area where TH may offer benefits in the management of SAH.

In our investigation of the impact on functional outcomes, seven studies were reviewed [13-21]. Excluding one RCT, the remaining studies exhibited a moderate to high risk of bias in participant selection and confounding factors. Additionally, there was considerable heterogeneity in the hypothermia protocols, including variations in induction time, hypothermia duration, rewarming rate, cooling methods, and the interval from symptom onset to cooling initiation. Some studies included cases with refractory ICP that underwent craniectomy [16,21], while others involved coiling alone [15,20]. However, a common practice across these studies was the application of TH at or below 35 °C after securing aSAH. The sole RCT investigating functional outcomes in aSAH patients initiated TH within 12 hours of symptom onset, maintained it at 34.5 °C for 48 hours, and employed a gradual rewarming rate of 0.5 °C every 12 hours [18]. Nevertheless, the three-month functional outcome did not achieve statistical significance, with a P-value of 0.06. Interestingly, the sole study showing statistical significance in favor of TH applied the intervention for about five days, highlighting a variation in the duration of the TH protocol [20]. This suggests that there is still a need to establish an appropriate protocol for TH.

In a study investigating the effects of TH on vasospasm in patients with aSAH, four papers were reviewed [17-20]. Except for one, none showed statistical significance, but the differences in occurrence rates between the groups suggested potential benefits. Kuramatsu et al. [17] demonstrated a significant reduction in mean middle cerebral artery velocities in the TH group compared to the standard care group using transcranial Doppler. Muroi et al. [13] explained that TH could reduce inflammation by decreasing the secretion of inflammatory cytokines such as interleukin (IL)-6, IL-1β, and tumor necrosis factor-α. Similarly, the studies discussed the potential for a reduction in DCI through TH's neuroprotective properties

[17,18,21]. Regarding mortality, although there are reports of an increase in mortality due to adverse events when applied to critically ill patients [27], this analysis indicated a trend towards reduced mortality with TH (RR, 0.74; 95% CI, 0.35–1.56). For SAH-induced hydrocephalus, there is still no significant evidence of effectiveness, and research in this area is insufficient. Thus, the effectiveness of TH in aSAH patients still requires further investigation.

The most significant challenge in maintaining TH effectively is the control of shivering. Since the publication of a document in 2008 introducing "the bedside shivering assessment modulation," the importance of shivering control in TH has gained significant attention [28]. The document notes that when shivering is not controlled, it can actually lead to an increase in resting energy expenditure and oxygen consumption. Five studies implemented a sedation protocol to address shivering control, with three of them suggesting the potential for improved functional outcomes in TH [13,17,18,20]. However, in the remaining study, which focused on patients with severe brain injuries categorized under Hunt & Hess Scale 5 and WFNS scale 5 (Glasgow Coma Scale score <7), both the group that received TH and the group that did not showed extremely poor prognoses [21].

In the past, TH was associated with increased risks of complications such as prolonged sedation, extended mechanical ventilation duration, prolonged intensive care unit stay, hypotension, and infection [2,29,30]. In the nine studies included in this investigation, five of them examined complications associated with TH. While these studies investigated different complications, they collectively did not show a significant difference in the occurrence rates of internal medical complications such as pneumonia, infection, blood pressure abnormalities, arrhythmia, or electrolyte imbalances [16-18,20,21]. One study reported an increase in hospital stay length as a complication of TH [16], but another literature review did not reveal a significant difference [17]. Unlike earlier reports of frequent complications associated with, TH recent advances in bundle management, adjustments based on predictive factors, and the adoption of protocols that maintain the target temperature above 33 °C have led to a reduction in the incidence of complications related to TH [31,32].

According to recent guidelines for the treatment of aSAH, it is mentioned that hypothermia during surgery for patients with Good grade SAH has not been proven effective [10]. These guidelines suggest that TH might only benefit a carefully selected group of patients who have poor grade SAH. Further-

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more, the importance of fever control has been highlighted in cases of refractory fever occurring in aSAH patients. However, the effectiveness of TH remains uncertain [10]. It's worth noting that meta-analyses of TH in conditions other than aSAH, such as ICH, TBI, and ischemic stroke, have also failed to demonstrate significant improvements in functional outcomes [6-9]. While there is one meta-analysis examining the efficacy of TH in aSAH, it includes intraoperative TH and normothermia, lacks clear references, and does not conduct a systematic review [33].

Therefore, our study was conducted with a focus on specific eligible criteria to accurately assess the effects of TH. This analysis, focusing on patients with poor-grade SAH treated with TH at or below 35 °C, was conducted with careful attention to study quality, variability in study designs, and the heterogeneity of the included studies. Future research, particularly large-scale RCTs, will be essential in further elucidating the utility of TH. Additionally, exploring the importance of fever control and the potential benefits of normothermia in aSAH management should be topics for future investigation. In our systematic review and meta-analysis, several limitations warrant careful consideration. The included studies demonstrated variability in design, and some had small sample sizes, potentially affecting the robustness of our conclusions. Notable heterogeneity in TH protocols across these studies further complicated the analysis. Additionally, due to inherent complexities and biases in combining RCTs and NRS in a single meta-analysis, we conducted separate analyses for these groups in a sensitivity analysis [34].

However, with only one RCT available, our focus was primarily on NRS. It was observed that the outcomes from the NRS did not significantly differ from those seen in the combined analysis of all studies, suggesting a consistent trend across different study designs. Our funnel plot analysis, guided by the Cochrane Handbook (version 5.1), included seven studies and did not indicate publication bias [34]. Nonetheless, with fewer than 10 studies, there is reduced power to effectively distinguish between chance and real asymmetry, potentially impacting the reliability of this conclusion. These aspects underscore the need for cautious interpretation of our findings and highlight the complexities involved in synthesizing diverse research methodologies.

In the field of neurocritical care, it is often difficult to establish strong recommendations based on systematic reviews or meta-analyses for specific conditions and topics. This challenge stems from a scarcity of randomized clinical trials and a lack of well-organized prospective studies on specific subjects. Therefore, guidelines are challenging to establish for certain conditions, and often the level of evidence remains relatively low. We share the regret that our study also faced difficulties in overcoming these obstacles. However, recent research has synthesized more comprehensive data, verified the effects on vasospasm occurrence, and improved the certainty of the evidence through better analysis. Although our findings align with prior research, our study verified the impact on certain complications and refined the analytical methodology. This improvement contributes positively to the neurocritical care field. Despite the existing limitations, we are hopeful that these incremental advancements will help deliver high-quality clinical guidelines, ultimately improving patient outcomes in critical care.

The results of this systematic review and meta-analysis suggest that the effectiveness of TH in patients with aSAH is primarily observed in its potential to impact vasospasm. However, the current evidence does not provide conclusive insights into the effects of TH on key aspects such as functional outcomes, DCI, hydrocephalus, and mortality. Therefore, further research is needed to comprehensively understand and substantiate the role of TH in the management of aSAH.

CONFLICT OF INTEREST

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

FUNDING

ACKNOWLEDGMENTS

None.

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SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4266/acc.2024.00612.

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Comparison of factors influencing the decision to withdraw life-sustaining treatment in intensive care unit patients after implementation of the Life-Sustaining Treatment Act in Korea

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Background: The decision to discontinue intensive care unit (ICU) treatment during the end-of-life stage has recently become a significant concern in Korea, with an observed increase in life-sustaining treatment (LST) withdrawal. There is a growing demand for evidence-based support for patients, families, and clinicians in making LST decisions. This study aimed to identify factors influencing LST decisions in ICU inpatients and to analyze their impact on healthcare utilization.
Methods: We retrospectively reviewed medical records of ICU patients with neurological disorders, infectious disorders, or cancer who were treated at a single university hospital between January 1, 2019 and July 7, 2021. Factors influencing the decision to withdraw LST were compared between those who withdrew LST and those who did not.
Results: Among 54,699 hospital admissions, LST was withdrawn in 550 cases (1%). Cancer was the most common diagnosis, followed by pneumonia and cerebral infarction. Among ICU inpatients, LST was withdrawn from 215 (withdrawal group). The withdrawal group was older (78 vs. 75 years, P=0.002), had longer total hospital stays (16 vs. 11 days, P<0.001), and higher ICU readmission rates than the control group. There were no significant differences in the healthcare costs of ICU stay between the two groups. Most LST decisions (86%) were made by family.
Conclusions: The decisions to withdraw LST of ICU inpatients were influenced by age, readmission, and disease category. ICU costs were similar between the withdrawal and control groups. Further research is needed to tailor LST decisions in the ICU.

Key Words: cancer; death; healthcare cost; intensive care unit; palliative care; terminal care

Original Article

INTRODUCTION

Since the Life-Sustaining Treatment (LST) Decision Act [1] was implemented in Korea in Feb-

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ruary 2018, the withdrawal or withholding of LST has become a form of death for patients in the intensive care unit (ICU). The LST Decision Act consists of two parts. The first part stipulates the requirements and procedures for terminating LST in patients at the end of life. The second part deals with hospice and palliative care. Our aim in this paper was to determine the effects of the first part of the law, including those on healthcare costs. Due to the enormous medical expenses possible at the end-of-life (EOL) stage [2], one of the aims of the LST Decision Act was to reduce futile treatments and decrease medical expenses. Since the law stipulates that EOL is a condition for which terminating LST is permissible, the ICU is a likely location of such termination. Furthermore, as seven intensive care criteria listed in the law are mostly performed in the ICU, it is valid to examine the pattern of medical usage in the ICU to determine the effect of enforcement of the law.

Increasingly, LST decisions are being made in ICUs, not only for patients with terminal cancer, but also for patients in catastrophic condition with various diseases [3,4]. However, the rates of advance preference for or refusal of LST by the patient and LST planning are low, and withdrawal of LST by decision of the family is common in critically ill patients nearing EOL [5-7]. This can deprive the patient of the opportunity to choose a dignified death, and family members may make a decision that is different from the patient's own intentions and disease condition [8,9]. Furthermore, relying on family members to make EOL decisions can be psychologically and ethically burdensome [10] and may delay the timing of withdrawal of LST for patients who are unlikely to recover despite treatment [11].

Healthcare providers involved in decisions regarding LST are hampered by a lack of evidence [5,8,11]. As the LST Act becomes more widely implemented, there is a need for guidelines to help clinicians make EOL decisions for critically ill patients under ICU care and to help the patient and their family with EOL planning, especially in acute and critical conditions like neurological and infectious disorders.

From the beginning of critical care medicine, the main treatment goals in the ICU have been to reduce mortality and prolong life [12]. Consequently, a large proportion of healthcare spending tends to be concentrated on elderly, EOL, and terminally ill patients [13-15]. The increasing challenges posed by limited healthcare resources due to an aging population or pandemics have hindered the efficient management and distribution of medical resources, particularly in the ICU [14,16,17]. Therefore, it is essential to determine whether there are differences in healthcare utilization behaviors and final

KEY MESSAGES

■ Older age, frequent intensive care unit (ICU) readmissions, cancer, and infectious disorders significantly influence the decision to withdraw life-sustaining treatment (LST) in ICU patients.

■ Although total healthcare costs were higher for the LST withdrawal group, ICU costs remained similar between patients who withdrew LST and those who did not, possibly due to reduced intensive care following withdrawal.

■ Decision-making regarding LST withdrawal was mostly determined by family members and varied depending on the disease, highlighting the need for personalized LST decision plans for critically ill patients.

medical expenses between critically ill patients who receive LST and those who do not.

This study aimed to identify factors that influence the decision to withdraw LST for patients admitted to the ICU, including age, disease, and identity of the decision maker. Furthermore, we investigated how the decision to withdraw LST affects the actual use of medical services by evaluating healthcare costs.

MATERIALS AND METHODS

Study Design and Data Sources
This study evaluated the effect of the LST act on ICU inpatients and identified determinants of LST withdrawal. We retrospectively reviewed the electronic medical records of patients who registered a determination form for LST withdrawal and the EOL process in a single tertiary hospital from January 1, 2019, to July 7, 2021. Factors influencing the LST withdrawal decision such as age, sex, disease, and identity of the decision maker were collected for comparison. Patients who withdrew LST according to the LST Decision Act were assigned to the withdrawal group and patients who did not were assigned to the control group. The control group comprised ICU inpatients who exhibited unstable vital signs and symptoms upon admission consistent with entering the EOL stage within the same study period as the withdrawal group. In the withdrawal group, the most prevalent disease categories were neurological disorders, infectious disorders, and cancer. For disease-matched comparison, the control group comprised ICU inpatients diagnosed with one or a combination of these three categories

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of disorders using International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes. Detailed diagnoses for each category are provided in Supplementary Table 1.

The Glasgow coma scale to assess mental state and the Acute Physiology and Chronic Health Evaluation (APACHE) II score were collected on admission to the ICU to gauge patient severity. Mortality was the primary outcome. Total hospital and ICU stays, readmission rate, and types of intensive care (cardiopulmonary resuscitation, hemodialysis, chemotherapy, mechanical ventilation, vasopressors, extracorporeal life support, and blood transfusion) were compared between the LST withdrawal and control groups. In the withdrawal group, days from admission to LST withdrawal decision and days from LST withdrawal decision to death were calculated. Furthermore, it was noted whether the patient or family made the decision on LST. Healthcare cost data of the groups were compared separately for total length of hospital stay and ICU stay.

Definitions and Process of LST

According to the LST Decision Act, withdrawal of LST can be implemented only during the EOL stage. EOL implies imminent death without the possibility of recovery or revitalization despite proper treatment. EOL was determined by the physician in charge and one medical specialist in the relevant field. LST was defined as medical treatment that merely extended the duration of the EOL process without curative effect. When this research was conducted, the legal definition of LST included mechanical ventilation, hemodialysis, vasopressors, and blood transfusion, common in the ICU setting. The difference between LST and usual ICU care is based on whether the patient is in the EOL stage or not. The decision to terminate LST was made by self or family (spouse and linear ascendants or descendants) in all analyzed patients. In the ICU, patients are often incapable of self-determining withdrawal of LST due to lack of consciousness. In this case, two or more identical statements from the family members on the patient's intention or unanimous consent of all family members were required.

Statistical Analysis

Categorical data are presented as proportions, normally distributed continuous data as means with standard deviations, and non-normally distributed continuous variables or ordinal variables as medians with interquartile ranges. Characteristics of subjects were summarized using descriptive statistics. Factors regarding the decision to withdraw LST first were subject-ed to univariate analysis, and then multivariate analysis was performed using a logistic regression model for variables with P-values less than 0.1. Student t-test and Fisher's exact test were used to assess the significance of differences in continuous and categorical variables between groups, respectively. To compare the three disease categories, the Kruskal-Wallis test was applied. Two-tailed P-values less than 0.05 were considered significant, and all statistical analyses were performed using R version 4.1.1 (R Foundation for Statistical Computing).
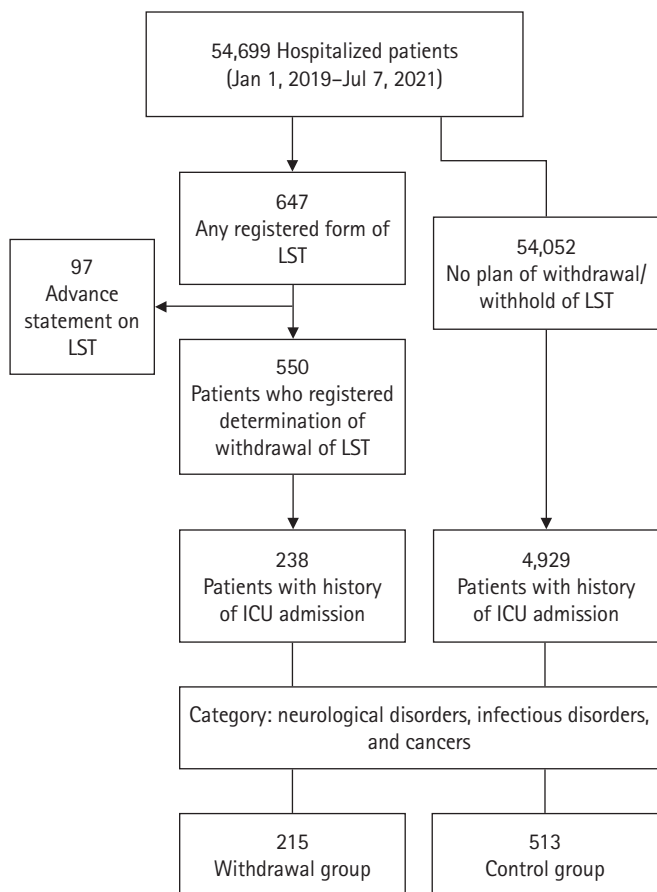
Ethics Statement

The study was approved by the Institutional Review Board of Ewha Womans University Seoul Hospital (No. SEUMC 2021-08-002-002, August 24, 2021), and the requirement for informed consent was waived due to the retrospective design of the study. The procedures in this study were performed in accordance with the ethical standards of the responsible committee on the privacy of individuals and secure data.

RESULTS

Characteristics of the Study Population

A total of 54,699 patients was admitted to the hospital during the study period, and 550 (1%) of these patients registered to withdraw from LST (Figure 1). In the total LST population, the median age was 78 years (interquartile range [IQR], 69–85 years), and 318 patients were male (58%). Cancer was the most common causative disease in patients who withdrew from LST, followed by pneumonia and cerebral infarction (Table 1). Among cancers, lung, biliary, and stomach cancers were the most common in descending order (Supplementary Figure 1A). Among patients who registered for an LST plan, 238 (238/550, 43%) had a history of ICU admission, of whom 90% (215/238) had a diagnosis of neurological disorder, infectious disorder, or cancer. These 215 patients were labeled as the withdrawal group. After matching the disease categories, the number of control group patients was 513 (Figure 1).

Median age of all ICU inpatients was 77 years (IQR, 64–84 years), and withdrawal group patients were significantly older than control group patients (78 vs. 75 years, P=0.002) (Table 2). There was no significant difference in the number of men or women in the withdrawal versus control groups. The most common disease in the ICU LST withdrawal group was cancer, as it was in the total population of LST withdrawal patients. Unlike the total population of LST withdrawal patients, the most common type of cancer in ICU inpatients was brain can-

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54,699 Hospitalized patients
(Jan 1, 2019–Jul 7, 2021)
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647
Any registered form of
LST
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54,052
No plan of withdrawal/
withhold of LST
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97
Advance
statement on
LST
```

```
550
Patients who registered
determination of
withdrawal of LST
```

```
238
Patients with history
of ICU admission
```

```
4,929
Patients with history
of ICU admission
```

```
Category: neurological disorders, infectious disorders,
and cancers
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215
Withdrawal group
```

```
513
Control group
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Figure 1. Distribution of diseases between patients for whom life-sustaining treatment was withdrawn and the control group. Patients in the life-sustaining treatment (LST) group and control group were assigned to one of three common critical disease categories of neurological disorders, infectious disorders, and cancers. The proportion of cancer patients was significantly higher in the withdrawal group than the control group. Conversely, the numbers of patients with neurological disorders and infectious disorders were higher in the control group than the withdrawal group. ICU: intensive care unit.

Table 1. Diseases of the patients who withdraw LST between the total population and ICU inpatients

Variable	Total withdrawal LST (n=550)	Withdrawal LST in ICU (n=238)
Cancer	190 (35)	50 (21)
Pneumonia	73 (13)	15 (6)
Cerebral infarction	54 (10)	45 (19)
Septic shock	35 (6)	22 (9)
CNS (SE, encephalitis, PD, dementia, etc.)	30 (5)	22 (9)
Intracerebral hemorrhage	28 (5)	27 (11)
Pulmonary (ARDS, TB, IPF, etc.)	25 (5)	10 (4)
Cardiopulmonary arrest	20 (4)	10 (4)
Subdural hemorrhage	20 (4)	13 (5)
Renal failure	14 (3)	1 (0)
Gastrointestinal disorders (bleeding, etc.)	11 (2)	3 (1)
Subarachnoid hemorrhage	11 (2)	10 (4)
Hepatobiliary disorders	10 (2)	4 (2)
Genitourinary disorders	6 (1)	0
Chronic obstructive pulmonary disease	6 (1)	2 (1)
Heart failure	5 (1)	2 (1)
Femur fracture	4 (1)	0
Myocardial infarction	3 (1)	1 (0)
Aortic aneurysm	1 (0)	0
General surgery related disorders	1 (0)	1 (0)
Idiopathic thrombocytopenic purpura	1 (0)	0
Superior mesenteric artery syndrome	1 (0)	0
Systemic sclerosis	1 (0)	0

Values are presented as number (%).
LST: life-sustaining treatment; ICU: intensive care unit; CNS: central nervous system; SE: status epilepticus; PD: Parkinson disease; ARDS: acute respiratory distress syndrome; TB: pulmonary tuberculosis; IPF: idiopathic pulmonary fibrosis.

cer (Supplementary Figure 1B). Furthermore, neurological disorders such as cerebral infarction and intracranial hemorrhage were more common in patients who withdrew from LST in the ICU than those that withdrew from LST outside the ICU (Table 2). APACHE II scores (25 [IQR, 20–34] vs. 27 [IQR, 20–34], P=0.82) and GCS (7 [IQR, 4–11] vs. 8 [IQR, 4–13], P=0.10) were not significantly different between patients in the withdrawal and control groups (Table 2).

When the three disease categories were compared, the proportion of cancer patients was significantly higher in the withdrawal group than the control group (P<0.001) (Table 2). Conversely, the numbers of patients with neurological or infectious disorder were higher in the control group than the withdrawal group (P=0.80, P<0.001, respectively). Overall, more ICU treatments were performed in the control group, while the withdrawal group received significantly fewer vasopressor treatments, hemodialysis procedures, and cardiopulmonary resuscitations than the control group, as shown in Table 2 and Figure 2.

Outcomes

Total hospital stay was significantly longer in the withdrawal group than the control group; however, there was no difference in ICU stay between these two groups (total hospital stay: 16 days [IQR, 8–27] vs. 11 days [IQR, 4–24], P<0.001; ICU stay: 7 days [IQR, 2–16] vs. 7 days [IQR, 2–18], P=0.59) (Table 3). Among patients who died during hospitalization (439/728,

Table 2. Demographics of withdrawal of life-sustaining treatment group and control group in ICU patients with three disease categories

Variable	Total (n=728)	Withdrawal (n=215)	Control (n=513)	P-value
Age (yr)	76 (64–84)	78 (69–83)	75 (63–84)	0.002
Sex				0.29
Female	322 (44)	102 (47)	220 (43)	
Male	406 (56)	113 (53)	293 (57)	
Disease				
Neurological disorder	436 (60)	127 (59)	309 (60)	0.80
Infectious disorder	206 (28)	38 (18)	168 (33)	<0.001
Cancer	86 (12)	50 (23)	36 (7)	<0.001
Severity				
APACHE II score	26 (20–34)	25 (20–34)	27 (20–34)	0.82
GCS score	8 (4–12)	7 (4–11)	8 (4–13)	0.10
Types of intensive care				
Mechanical ventilator	449 (62)	122 (57)	327 (64)	0.08
Vasopressor	447 (61)	115 (53)	332 (65)	0.01
Transfusion	348 (48)	92 (43)	256 (50)	0.09
Hemodialysis	134 (18)	25 (12)	109 (21)	0.002
CPR	72 (10)	7 (3)	65 (13)	<0.001
Chemotherapy	34 (5)	9 (4)	25 (5)	0.22
ECLS	5 (1)	0 (0)	5 (1)	0.33

Values are presented as median (interquartile range) or number (%).
ICU: intensive care unit; APACHE: Acute Physiology and Chronic Health Evaluation; GCS: Glasgow Coma Scale; LST: life-sustaining treatment; CPR: cardiopulmonary Cardiopulmonary resuscitation; ECLS: extracorporeal life support.
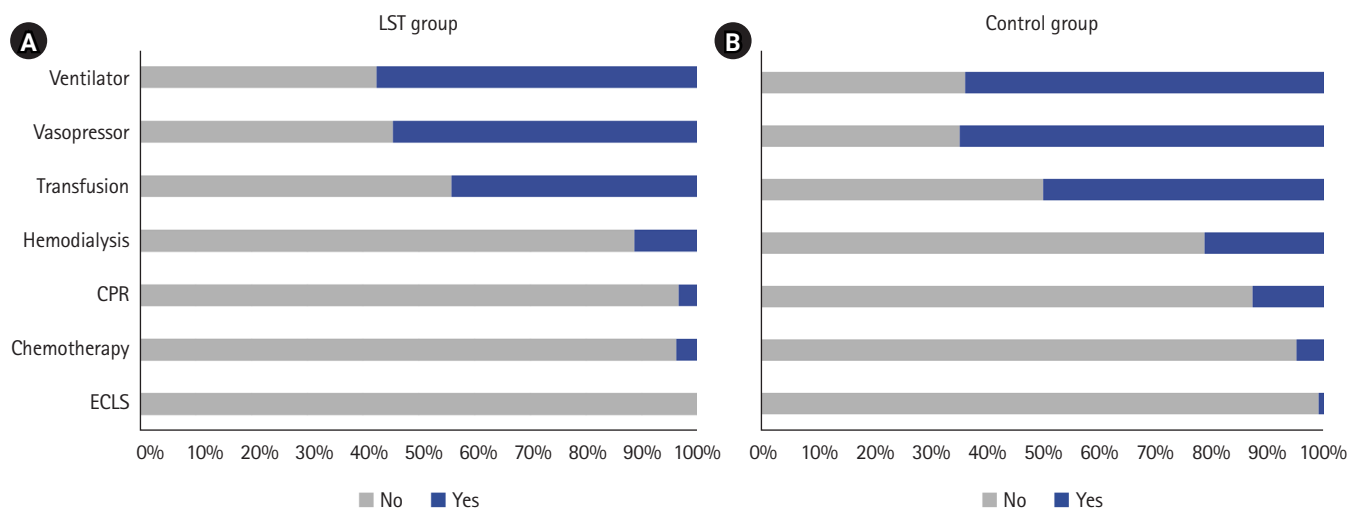
Figure 2. Types of intensive care performed in the life-sustaining treatment (LST) withdrawal group (A) and control group (B) during their intensive care unit stay. The legal definition of LST includes not only cardiopulmonary resuscitation (CPR), but also mechanical ventilation, hemodialysis, vasopressors, and blood transfusion, which are commonly performed in intensive care units. The most common intensive care received during the intensive care unit stay among those who withdrew LST was, in order of frequency, mechanical ventilation, vasopressor usage, and blood transfusions. ECLS: extracorporeal life support.

60%), the time from admission to death was significantly shorter in the control group (8 days [IQR, 2–19]) than in the withdrawal group (14 days [IQR, 6–28]). A longer hospital stay but a shorter time from LST withdrawal to death were observed in the withdrawal group (16 days [IQR, 8–27] and 2 days [IQR, 0–7], respectively). Readmission rates during the study period were significantly higher in the withdrawal group than the control group (24% vs. 13%, P<0.001).

To determine the factors that affected the decision to withdraw LST, age, readmission, hospital stay, diagnosis of cancer, and infectious disorders were analyzed by multivariate logistic regression (Table 4). After adjusting for relevant factors, older age (odds ratio, 1.019; 95% confidence interval, 1.007–1.032; P=0.002) and higher readmission rate (odds ratio, 1.760; 95% confidence interval, 1.128–2.733; P=0.01) significantly affect-

ed the decision to withdraw from LST in the ICU. Regarding disease category, cancer patients were 3.3-fold more likely to withdraw from LST than control patients. In contrast, patients with infectious disorders tended to be twice as likely not to withdraw from LST as cancer patients and those with neurological disorders.

Comparison of Healthcare Costs between the Withdrawal and Control Groups

To assess if the decision to withdraw LST affected healthcare costs, we compared overall hospitalization costs and ICU costs for the withdrawal and control groups (Table 3). Overall hospitalization costs were higher in the withdrawal group than the control group, but there was no significant difference in ICU costs between these two groups. The higher overall cost of

Table 3. Outcomes and healthcare costs between the withdrawal of LST group and control group

Variable	Total (n=728)	Withdrawal (n=215)	Control (n=513)	P-value
Hospital stay (day)	12 (5–24)	16 (8–27)	11 (4–24)	<0.001
ICU stay (day)	7 (2–18)	7 (2–16)	7 (2–18)	0.59
Admission to death (day)	10 (3–22)	14 (6–28)	8 (2–19)	<0.001
Admission to LST (day)		8 (3–20)		
LST to death (day)		2 (0–7)		
Readmission	118 (16)	52 (24)	66 (13)	<0.001
Mortality	439 (60)	141 (66)	298 (58)	0.07
Healthcare cost (KRW)				
Total admission	25,399,018 (11,389,713–49,619,676)	29,853,224 (13,697,848–53,778,748)	20,855,966 (9,247,913–45,047,298)	0.001
ICU	14,672,692 (7,308,024–32,439,968)	15,781,577 (8,138,538–32,571,558)	14,349,285 (6,908,488–32,438,511)	0.35
From ICU to LST withdrawal[a]		12,949,487 (6,437,354–27,491,472)		
From LST withdrawal to discharge[b]		282,659 (0–4,586,083)		

Values are presented as median (interquartile range) or number (%).
ICU: intensive care unit; LST: life-sustaining treatment; KRW: Korean Won.
a) ICU-LST: from ICU admission to withdrawal of LST; b) LST-discharge: from withdrawal of LST to discharge.

Table 4. Multivariate analysis of factors affect to decision of withdrawing life-sustaining treatment in patients admitted ICU

Variable	Univariate		Multivariate	
	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Age	1.014 (1.003–1.026)	0.01	1.019 (1.007–1.032)	0.002
Hospital stay	1.005 (1.000–1.011)	0.06	1.004 (1.000–1.010)	0.19
Readmission	2.130 (1.441–3.240)	<0.001	1.760 (1.128–2.733)	0.01
Infectious disorder	0.441 (0.297–0.655)	<0.001	0.509 (0.332–0.765)	0.001
Cancer	4.015 (2.526–6.383)	<0.001	3.318 (2.046–5.430)	<0.001

ICU: intensive care unit; CI: confidence interval.
P-values were calculated by logistic regression.

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hospitalization in the withdrawal group was related to a longer length of stay. Narrowing of the cost gap between the two groups during the ICU stay indicates that withdrawal of LST reduces the number of medical procedures and treatments, which impacts healthcare costs. The median cost from LST withdrawal day to discharge day was 1% of the median total ICU cost.

Identity of Decision Makers of Withdrawal of LST in ICU Patients

To identify the primary decision maker regarding withdrawal from LST in EOL patients in the ICU, we compared the proportion of patients who self-determined withdrawal from LST versus family determination. In most cases, family members made the decision (184/215, 86%), and there was significant difference by disease category, occurring in 89% and 95% of respective families of patients with neurological disorders and infectious disorders (Figure 3). In contrast, 30% of patients with cancer made their own decisions, a higher rate than for other disease categories (P<0.001).

DISCUSSION

This study focused on withdrawal of LST in patients admitted to the ICU after implementation of the LST Decision Act in Korea in 2018. Patients for whom LST was withdrawn were older, had longer hospital stays, more ICU readmissions, and higher overall healthcare costs than those who did not. However, there was no difference in the cost of the ICU stay between patients in the withdrawal and control groups. This might be

explained by death within 2 days after withdrawal of LST. Furthermore, the withdrawal group received significantly less intensive care, including the use of vasopressors, hemodialysis, and cardiopulmonary resuscitation, than the control group. There were different patterns in the decision to withdraw LST among cancer, infectious disease, and neurological disorder patients.

Communication with patient families needs to be improved as they are making most LST decisions. According to a previous study [18], participating in proactive family conferences resulted in less exposure of patients to non-beneficial interventions than participation in standard doctor-family conferences. The percentage of bereaved families experiencing negative emotions such as anxiety, depression, and symptoms of post-traumatic stress also decreased significantly more after proactive family conferences than standard conferences. Depending on the nature of disease, a patient may be unable to make LST decisions. Therefore, it is essential to have a process in place to reduce the ethical and psychological burden of family members. Caregivers or families of patients may request information about withdrawal of LST in the early phase of ICU care, but unexpected such decisions can be challenging. Given the uncertainty in determining the optimal time for LST withdrawal, early decisions regarding LST may compromise the commitment to appropriate intensive treatment rather than respecting the patient's will. Therefore, identified factors that influence the decision to withdraw from LST can provide useful information for decision-makers.

In our study, 30% of patients (215/728) admitted to the ICU for neurological disorders, infectious disorders, or cancer
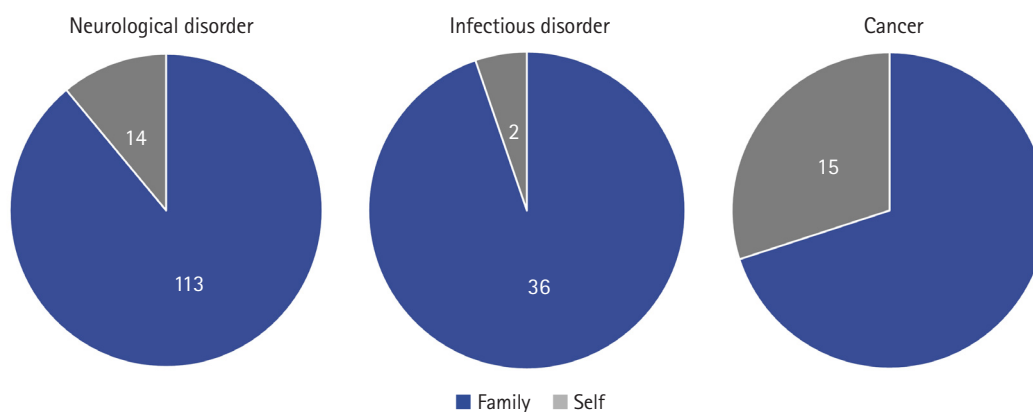
Figure 3. Identity of decision-makers to withdraw life-sustaining treatment among intensive care unit inpatients. Overall, withdrawal of life-sustaining treatment was predominantly by family determination, but it varied by the nature of the disease: self-determination was higher for cancer patients compared to other diseases and lower for neurological disorders with altered consciousness and sepsis with the possibility of rapid deterioration.

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decided to terminate LST. The percentage of patients who withdrew from LST was remarkably higher in these critically ill patients compared to all inpatients (1%). This suggests that research is needed on an LST withdrawal process more suitable for critically ill patients.

Age was a significant factor in the decision to withdraw LST regardless of severity. Disease was also a significant factor in the LST withdrawal decision, with cancer in particular being a notable predictor. Infectious disorders were associated with a lower rate of LST withdrawal than cancer and neurological disorders. This discrepancy may be due to the shorter hospital stay of patients with infectious diseases and septic shock than that of those with cancer or neurological conditions. Loss of consciousness due to neurological disorders or abrupt aggravation of infectious disorders might be a barrier to self-determination of LST. This is because of the limited time available for deciding on LST withdrawal in patients with rapidly deteriorating infectious disorders, as well as the inclination of cancer patients to autonomously choose to withdraw LST. Consequently, patients at high risk of impending death in the ICU, especially elderly patients, require a wide range of advance care planning methods, including LST planning.

Hospitalization duration, overall hospitalization costs, and readmission rates were significantly higher in the withdrawal group than the control group. This can be attributed to prolonged disease aggravation or a delay in the decision to withdraw LST. The higher rate of ICU readmissions in the withdrawal group indicates that patients in this group may have gradually deteriorated, received repeated ICU care, and eventually decided to discontinue ongoing treatment. This may also have contributed to the longer length of hospital stay in the withdrawal group than the control group. The lack of difference in ICU costs between the two groups is likely because costs rapidly decrease after the decision to withdraw LST. In a similar vein, the notably low ICU costs and days from LST withdrawal to discharge provide support for the effectiveness of withdrawing or withholding LST in reducing both ICU costs and utilization. For these reasons, patients admitted to the ICU need information about prognosis and optimal timing of EOL care preparation, and the patient's family should be involved from admission to the ICU. An appropriate approach to optimal timing and prediction of prognosis is important not only because it would help patients make their own decisions, but also because it would have economic efficacy.

Intensive care was provided more frequently in the control group than the withdrawal group, particularly cardiopulmonary resuscitation, hemodialysis, and vasopressors. This difference suggests that the decision to withdraw LST is made when the patient requires an additional invasive procedure. This may be because the decision to withdraw LST is often made by family members who are afraid of invasive intensive care that may cause patient suffering. Physicians need to consider that the nature of intensive care, especially invasive procedures, may affect a family's decision. Moreover, non-invasive alternative treatments available in the general ward may help reduce the length of stay in the ICU while ensuring that patients receive adequate supportive care. The factors that determine when to discontinue types of intensive care were not addressed in this study and require further research.

The LST Decision Act is increasingly being applied in patients at EOL, but the decision to apply the law is often left to the individual doctors' judgment. It is necessary to find ways to better time LST decisions given the critical nature of patients entering the ICU. These measures include identifying prognostic indicators according to type of disease, providing prognostic information that can guide the LST decision, and explaining the option of withdrawing LST to patients and their families from the point of ICU admission.

This study has several limitations. First, since this was a single-center study with a retrospective research design, its generalizability to other cohorts is limited. However, it is meaningful to determine how the LST Decision Act has been applied in actual clinical settings since it became law. Second, despite efforts to classify patients into disease groups based on the primary cause of admission to the ICU, such patients may have overlapping diseases. Third, we did not distinguish between withdrawal and withholding of LST in this study, as these are treated the same in the LST Decision Act [8,19]. Fourth, the comprehensive criteria used to define the control group may have influenced the study results. The definition of EOL stage varies, and there is no clear single standard for predicting the exact EOL period. Upon admission to the ICU, unstable vital signs and symptoms can signal impending death and the EOL stage. As the main objective of this study was to examine factors influencing the decision to withdraw LST based on diagnosis upon ICU admission, patients admitted to the ICU due to unstable vital signs were assumed to be nearing the EOL stage and included in the control group. Additionally, in cases where caregivers refused to proceed with LST, the absence of an EOL assessment may have resulted in inclusion of such patients in the control group. Overcoming these limitations necessitates the establishment of realistic criteria for EOL assessment based

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on prospective future studies. Finally, by comparing medical expenses, we attempted to determine whether futile medical interventions were reduced by implementing the LST Decision Act. Though the healthcare costs in the ICU were similar in the withdrawal and control groups, the total healthcare cost was higher in the withdrawal group. This is probably because of delayed decision-making regarding withdrawal of LST after ICU admission and the longer hospital stay of the withdrawal group. Additionally, other factors affecting healthcare utilization such as religion, geographic region, and socioeconomic background were not considered in our analyses due to the retrospective nature of the study. Supporting our findings, a recent study reported a decrease in healthcare utilization among patients who chose withdrawal or withholding of LST compared to those who did not [20]. Further comprehensive and prospective research is warranted to delve into these factors.

We identified advanced age, frequent ICU readmissions, and cancer as significant factors in the ICU in the decision to withdraw LST. Given the nature of critically ill patients who are often incapable of making self-decisions due to rapid disease deterioration or a decline in mental status, there is a growing need for more targeted research on LST decisions in the ICU. Additionally, proper processes should be established to provide timely information after ICU admission to patients and their families to support them in their decision-making process. The findings of this study underscore the complex nature of LST decisions in the ICU, emphasizing the need for enhanced coordination in patient decision-making processes and allocation of healthcare resources. Further investigation is imperative to tailor LST decision-making in the ICU to support patients, caregivers, and ICU clinicians.

CONFLICT OF INTEREST

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

FUNDING

ACKNOWLEDGMENTS

None.

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AUTHOR CONTRIBUTIONS

Conceptualization: all authors. Methodology: CJK, KSH, JP. Formal analysis: KSH, JP. Data curation: KSH, JP. Visualization: JP. Writing–original draft: CJK, KSH, JP. Writing–review & editing: all authors.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4266/acc.2023.01130.

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Mortality rates among adult critical care patients with unusual or extreme values of vital signs and other physiological parameters: a retrospective study

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Background: We evaluated relationships of vital signs and laboratory-tested physiological parameters with in-hospital mortality, focusing on values that are unusual or extreme even in critical care settings.

Methods: We retrospectively studied Philips Healthcare–MIT eICU data (207 U.S. hospitals, 2014–2015), including 166,959 adult-patient critical care admissions. Analyzing most-deranged (worst) value measured in the first admission day, we investigated vital signs (body temperature, heart rate, mean arterial pressure, and respiratory rate) as well as albumin, bilirubin, blood pH via arterial blood gas (ABG), blood urea nitrogen, creatinine, FiO_2 ABG, glucose, hematocrit, PaO_2 ABG, $PaCO_2$ ABG, sodium, 24–hour urine output, and white blood cell count (WBC).

Results: In-hospital mortality was ≥50% at extremes of low blood pH, low and high body temperature, low albumin, low glucose, and low heart rate. Near extremes of blood pH, temperature, glucose, heart rate, PaO_2, and WBC, relatively. Small changes in measured values correlated with several-fold mortality rate increases. However, high mortality rates and abrupt mortality increases were often hidden by the common practice of thresholding or binning physiological parameters. The best predictors of in-hospital mortality were blood pH, temperature, and FiO_2 (scaled Brier scores: 0.084, 0.063, and 0.049, respectively).

Conclusions: In-hospital mortality is high and sharply increasing at extremes of blood pH, body temperature, and other parameters. Common-practice thresholding obscures these associations. In practice, vital signs are sometimes treated more casually than laboratory-tested parameters. Yet, vitals are easier to obtain and we found they are often the best mortality predictors, supporting perspectives that vitals are undervalued.

Key Words: acidosis; body temperature; fever; hypothermia; physiological parameters; vital signs

INTRODUCTION

In scoring systems, patient risk of mortality is commonly evaluated by combining information on vital signs, other physiological parameters, medical histories, and other attributes [1-5]. However, it is also of interest to understand how values of individual measurements are

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associated with mortality rates, particularly when the value of a physiological parameter is unusual or extreme. For example, if a measurement shows very unusually low blood pH, body temperature, or albumin level, how is that quantitatively associated with mortality rates? Here, we sought to address this question for adult critical care patients and the outcome of in-hospital death, focusing on physiological values that are unusual or extreme even relative to the standards of the critical care setting.

Many studies evaluate mortality associations for common and moderately unusual values of physiological parameters, but few studies evaluate extreme values [6-8]. We used the large-scale Philips Healthcare–MIT eICU database of electronic health records (EHR) to provide the especially large numbers of patient records that are necessary to study extreme values.

Several studies report that vital signs are often measured and recorded with less care than other physiological parameters, including laboratory-tested physiological parameters [9-11]. Consequently, it has been argued that vital signs are undervalued in nursing practice [9,10,12]. In light of this research, we also sought to compare results between vital signs and other physiological parameters.

The objective of this study was to evaluate associations between major physiological parameters and in-hospital mortality among adult critical care patients, focusing especially on unusual physiological values and the comparison of vital signs with other physiological parameters.

MATERIALS AND METHODS

Setting

We retrospectively studied adult critical care stays from the Philips Healthcare–MIT eICU database (version 2.0), which includes critical care stays at 208 U.S. hospitals during 2014–2015. The dataset consists of EHR routinely collected in the Philips eICU program, a multihospital telehealth system providing remote support to bedside clinical teams in the critical care setting. Year 2014–2015 Philips eICU EHR were prepared for research purposes by the Philips eICU Research Institute and the MIT Lab for Computational Physiology [13-17].

Ethical Approval

As a retrospective, secondary study of deidentified data made available publicly through the eICU program, this research required no ethics committee approval or additional patient

> **KEY MESSAGES**
>
> - Among adult critical care patients, in-hospital mortality rates exceed 50% at extremes of low blood pH, low and high body temperature, low albumin, low glucose, and low heart rate.
> - These high mortality rates become hidden or underestimated when physiological parameters are interpreted using common thresholds, cutoffs, bins, or categorizations.
> - Although vital signs are sometimes treated less carefully than laboratory-tested parameters, we found that vital signs are often the best mortality predictors, which supports the view that vital signs are undervalued in contemporary clinical practice.

consent.

Participants

The eICU database includes 175,091 stays that were (1) by patients aged ≥18 years and (2) admissions, readmissions, or transfers, rather than stepdown stays or other stay types. We excluded stays lacking discharge survival status (n=1,597, 0.9%) and/or collected physiological parameters for Acute Physiology Score III (APS-III) (n=6,535, 3.7%) [1,17]. At one of the 208 eICU hospitals, no stays met the study selection criteria, so this hospital was excluded. Altogether, application of study selection criteria left 166,959 stays by 132,513 patients at 207 hospitals for analysis.

Data Collection

All objective physiological parameters from APS-III were analyzed, including the four traditional vital signs (blood pressure, body temperature, heart rate, and respiratory rate) and 12 other physiological parameters [1]. For each physiological parameter, we analyzed the most deranged value measured during the first 24 hours of admission. Following APS-III, most deranged was defined as furthest from reference-range midpoints of albumin, 13.5 g/dl (*de facto* lowest considered worst); bilirubin, 0 mg/dl (highest considered worst); blood pH via arterial blood gas (ABG), 7.4; blood urea nitrogen, 0 mg/dL (highest considered worst); body temperature, 38 °C (100.4 °F); creatinine, 1.0 mg/dl; FiO_2 ABG, 21%; glucose, 130 mg/dl; heart rate, 75 beats/min; hematocrit, 45.5%; mean arterial pressure (average of systolic and diastolic pressure), 90 mm Hg; PaO_2 ABG, 80 mm Hg; $PaCO_2$ ABG, 40 mm Hg; respiratory rate, 19

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breaths/min; sodium, 145 mEq/L; 24-hour urine output, 10,00 mL (stays <24 hour excluded); and white blood cell count (WBC), 11.5 1000/μl.

Data Availability

The PhysioNet program (MIT Laboratory for Computational Physiology, MIT) makes all datasets analyzed in the current study publicly available subject to research use agreements and training requirements. The data sharing policy for this data source can be found at https://eicu-crd.mit.edu/ (date accessed: 2023-01-28). Code used in this study is available at https://doi.org/10.6084/m9.figshare.25596504.

Data Analysis

Splines were used to allow for nonlinear relationships [18,19]. Penalized cubic splines were fit in univariate logistic regressions using the R mgcv package, modeling the response variable as quasibinomial to account for overdispersion [20]. Confidence bands are 95% (pointwise) and account for uncertainty in spline degrees of freedom. In addition to analyses that used splines, a binned (i.e., categorized) analysis was performed to demonstrate the consequences of binning for risk prediction. Binning is standard practice in risk prediction systems that use physiological parameters. In the binned analysis, the values of physiological parameters were binned by quintiles and the mortality rate was evaluated in each bin.

For any analysis of big data, there is a question of what data range to plot since rare typos and mis-entries lead to a wide set of values beyond those that are relevant or clinically verifiable. Our aim was to plot the central range of the data where observations were sufficiently dense to support statistically informative estimates, and we selected this range by applying the criterion that widths of confidence bands from the main (continuous) analysis were required to be ≤25 percentage points.

Predictive performance was evaluated from spline estimates using scaled Brier scores, which are Brier scores rescaled to account for differences in outcome prevalence. These resemble Pearson's R^2 [21]. Higher values indicate better performance.

RESULTS

Overall Associations with In-hospital Mortality

Figure 1 shows the associations between 16 major physiological parameters and in-hospital mortality among adult patients during 166,959 critical care visits at 207 U.S. hospitals. When analyzing actual physiological values (continuous analysis),

the relationships were commonly nonlinear and often bathtub shaped—mortality rates increased at both very low and very high values of physiological parameters. For several parameters, unusual values were associated in-hospital mortality rates that exceeded 50%, including at extremes of blood pH, body temperature, glucose, heart rate, and albumin level.

In addition to analyzing values of physiological parameters as measured, we analyzed values binned (categorized) by quintiles (Figure 1). This was done to illustrate consequences of binning, which is often applied to physiological parameters. After binning, the bathtub-shaped relationships with mortality were no longer evident for several physiological parameters, including heart rate and hematocrit. Moreover, after binning, in-hospital mortality rates did not reach 50% for any physiological parameter. Binning reduced the maximum observed mortality rate by more than half for several physiological parameters, including blood pH, body temperature, glucose, heart rate, hematocrit, and WBC.

Abruptness of Changes in In-hospital Morality

For several physiological parameters, relatively small changes in measured values were associated with abrupt, several-fold increases in in-hospital mortality rates (Figure 1). These abrupt increases were most common at extreme physiological values. For example, reductions in glucose level from 50 to 10 mg/dl were associated with a 2.9-fold increase in mortality (21% [95% CI, 20%–22%] to 60% [95% CI, 56%–66%]), reductions in heart rate from 40 to 25 beats/min were associated with a 4.0-fold increase in mortality rate (12% [95% CI, 11%–13%] to 47% [95% CI, 44%–51%]), and reductions in WBC from 4,000 to 1,000/μl were associated with a 3.7-fold increase in mortality rate (9% [95% CI, 8%–9%] to 33% [95%, 31%–6%]). When binning was applied to the physiological parameters, all of these sharp changes in mortality rates were hidden.

Predictiveness for In-hospital Mortality

Of the physiological parameters, blood pH, body temperature, and FiO_2 were most predictive of in-hospital death (scaled Brier scores: 0.084, 0.063, and 0.049, respectively) (Table 1). However, predictive performance fell after binning (median performance loss, 36%) (Table 1). Binning caused the largest reduction of predictive performance for body temperature (performance loss, 68%) and the smallest reduction for urine output (performance loss, 4%).

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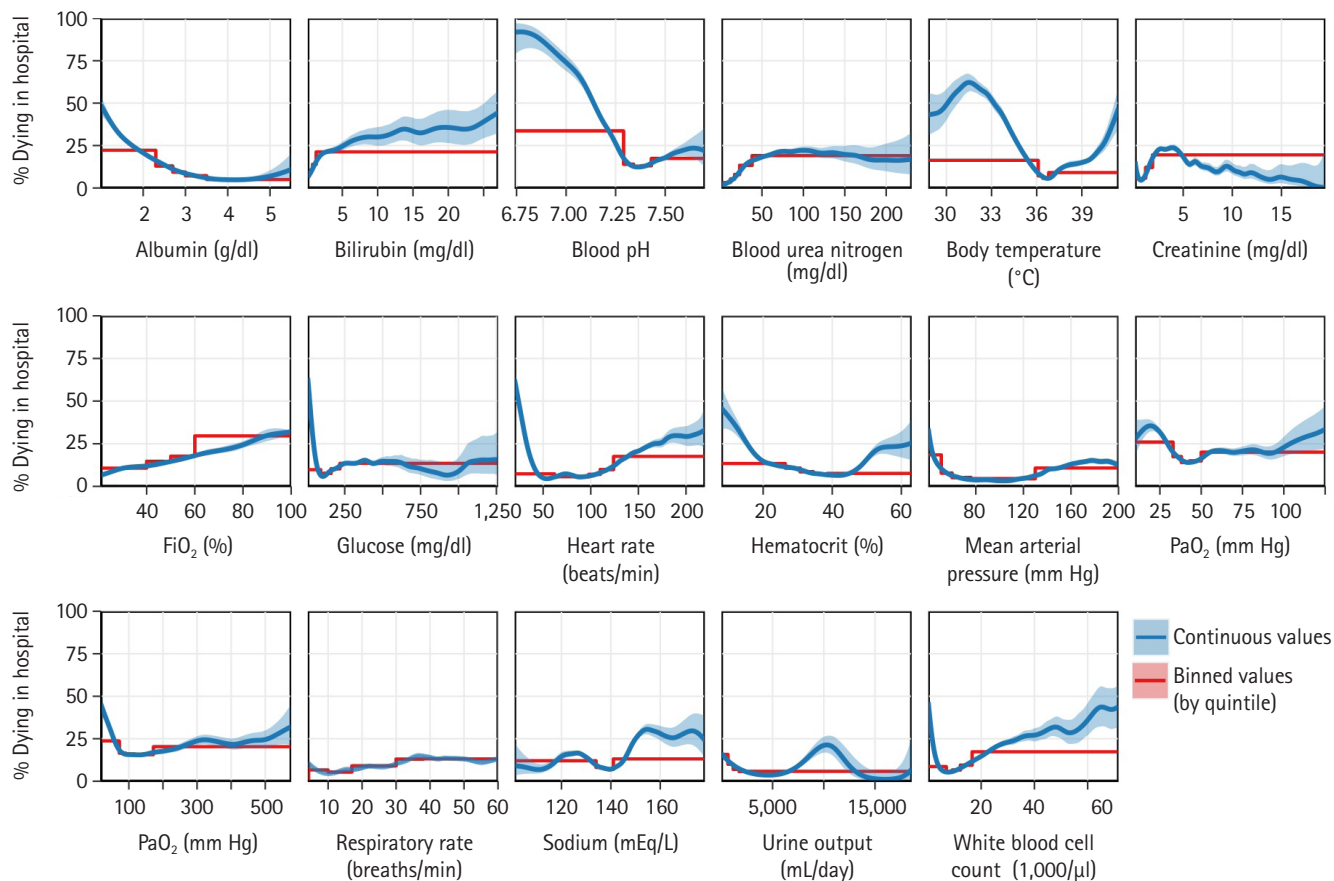
Figure 1. Physiological parameters in the first 24 hours and their associations with in-hospital death, as evaluated in the Philips Healthcare – MIT eICU database for 166,959 critical care admissions. Analyses of the exact values of physiological parameters (continuous analysis, blue lines) show that extreme values physiological parameters are often associated with high rates of in-hospital mortality. For example, in-hospital mortality rates reach at least 50% in patients who have unusual values of blood pH, body temperature, albumin level, and several other physiological parameters. However, common practice is to evaluate binned (i.e., categorized) values of physiological parameters, and when this is done (quintile-binned analysis, red lines), most of the elevations in mortality rates are hidden at unusual physiological parameter values. Confidence bands are 95% and are sometimes too narrow to be visible.

Comparison of Vital Signs with Other Physiological Parameters

On average, predictiveness for in-hospital mortality was better for traditional vital signs (body temperature, blood pressure, heart rate, and respiratory rate) than for other physiological parameters (mean of scaled Brier scores: 0.041 vs. 0.033). However, binning caused larger average reductions in predictive performance for vital signs than for other physiological parameters, with the result that binned vital signs had less overall predictive ability for in-hospital mortality than did other physiological parameters (mean of scaled Brier scores after binning: 0.021 vs. 0.023).

As expected, measurement availability in the first 24 hours of critical care admission was invariably better for vital signs than

for other physiological parameters (Table 1). Each vital sign was measured and recorded in EHR for at least 94% of patients. (It is probable that vital signs were taken for more patients, but the measurements may not have reached EHR.) Of the physiological parameters that are not vital signs, albumin level, urine output, bilirubin level, blood pH, FiO₂, PaCO₂, and PaO₂ were each available for less than 40% of patients. Considering the three physiological parameters that were most predictive of in-hospital morality, availability was 94% for body temperature but only 23% for blood pH and FiO₂.

DISCUSSION

In this study, we observed that in-hospital mortality rates were

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Table 1. Physiological parameters measured in the first 24 hours of critical care admission: availability of measurements and predictive performance for in-hospital mortality

Physiological parameter	Availability (%)[a]	Predictive performance		
		Continuous value[b,c]	Binned value[b,d]	Performance loss by binning (%)[e]
Albumin (g/dl)	39.6	0.048	0.038	21
Bilirubin (mg/dl)	35.9	0.029	0.022	23
Blood pH	23.2	0.084	0.044	48
Blood urea nitrogen (mg/dl)	79.1	0.041	0.039	5
Body temperature (°C)	94.0	0.063	0.020	68
Creatinine (mg/dl)	79.4	0.043	0.037	15
FiO_2 (%)	23.2	0.049	0.044	10
Glucose (mg/dl)	87.7	0.019	0.007	61
Heart rate (beats/min)	99.7	0.039	0.021	46
Hematocrit (%)	77.7	0.011	0.006	44
Mean arterial pressure (mm Hg)	99.5	0.048	0.031	35
$PaCO_2$ (mm Hg)	23.2	0.017	0.012	26
PaO_2 (mm Hg)	23.2	0.012	0.007	47
Respiratory rate (breaths/min)	99.2	0.014	0.011	20
Sodium (mEq/L)	79.8	0.018	0.007	61
Urine output (mL/day)	36.9	0.019	0.018	4
White blood cell count (1,000/μl)	75.6	0.039	0.020	49

a) The proportion of stays for which the physiological parameter was recorded in the first 24 hours of critical care admission; b) Predictive performance for in-hospital mortality is evaluated in terms of scaled Brier scores. Higher values indicate better predictive performance; c) In the analysis of continuous values, the actual value of the physiological parameter is used for risk prediction; d) In the analysis of binned values, the quintile-binned value of the physiological parameter is used for risk prediction instead of the actual value, mirroring common binning approaches in risk scoring systems. In both cases, performance is evaluated for the most deranged value of the physiological parameter measured in the first 24 hours of critical care admission; e) Performance loss is calculated as the percentage reduction in the scaled Brier score after binning.

especially elevated for adult critical care patients with very low blood pH, very low or high body temperature, very low glucose level, very low heart rate, or very low albumin level in the first 24 hours of admission to critical care. In-hospital mortality reached at least 50% in the extreme ranges of these physiological parameters. We also observed that, in some ranges of physiological parameters, relatively small changes in the physiological parameter value were associated with abrupt increases in in-hospital mortality rates. For example, tripling or quadrupling of in-hospital mortality rates was associated with reductions in glucose level from 50 to 10 mg/dl, heart rate from 40 to 25 beats/min, and WBC from 4,000 to 1,000/μl. Further, vital signs were on average better predictors of in-hospital mortality than were other physiological parameters, and vital signs had consistently better availability.

The novelty of these findings is their extension of previous research to unusual and extreme values of physiological parameters. Most studies are not large enough to analyze such unusual values. Others miss associations with high mortality

because they apply binning (i.e., categorization) procedures that mix extreme and more typical physiological parameters values together, diluting effects of the extreme values. Studies of patient risk scoring regularly bin, categorize, dichotomize, threshold, cutoff, or linearize the physiological parameters [1-5,22]. For example, Acute Physiology and Chronic Health Evaluation (APACHE) IV, Simplified Acute Physiology Score (SAPS) 3, and Mortality Probability Model 0-III (MPM0-III) all bin physiological values [1-4]. Our result demonstrate that binning obscures associations with high mortality (Figure 1), conceals bathtub-shaped (U-shaped) associations with mortality (Figure 1), hides abrupt mortality-rate increases that accompany small changes in some physiological parameter values (Figure 1), and greatly reduces the predictiveness for in-hospital mortality (Table 1). Further, binning produced larger average reductions in predictive performance for vital signs than for other physiological parameters. These findings support the view that it is best to avoid binning in mortality risk prediction and early warning score systems [19], especially for vital signs.

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Despite the limitations of binning, sophisticated risk scoring systems can still provide well-calibrated estimates of mortality risk because patients with an extreme value of one physiological parameter usually also have other mortality risk factors that are accounted for in the scoring systems. Nonetheless, we think there is value in seeing how high mortality rates climb at extremes of individual physiological parameters—for example, how in-hospital mortality rates more than tripled from 39 °C to 41.5 °C body temperature (15% vs. 50% mortality)—because these physiological parameter changes are observed in clinical practice before evaluation in risk scoring systems.

Binned values are also common in research studies, textbook introductions, and everyday practice. Perhaps because binning is ubiquitous, nurses, physicians, and researchers sometimes misinterpret results reported for binned physiological values as if they applied to all values of the underlying parameter that were binned together. For example, based on binned research, it is sometimes stated that body temperatures above thresholds like >38 °C and 40 °C are associated with no increase in mortality rates or with only moderate increases [12,23]. Yet, by performing unbinned analyses, we found that about half of critical care patients died at the highest ranges of body temperature (41.5 °C) (Figure 1). This is four times greater than the mortality rate suggested by binned analysis of the same data (Figure 1), demonstrating how binning can produce major errors in risk assessment.

Several articles conclude that vital signs are undervalued in clinical practice, especially in comparison with laboratory-tested physiological parameters [9,10,12]. Our results support the value of vital signs. For example, vital signs had better average predictiveness for in-hospital mortality than did other physiological parameters, even though measurements of vital signs cost less and are simpler to perform. However, binning reduced the average predictive ability of vital signs below other physiological parameters, which suggests that the ubiquity of binning may be one reason that vital signs are undervalued.

Prior studies also found that vital signs were taken and recorded with less care and accuracy than other physiological parameters, especially laboratory-tested parameters [9,11]. This suggests the actual predictiveness of vital signs might increase if they were measured more carefully. Better nursing practices and protocols may be able to improve vital sign measurement quality [10,11,24]. Of the four vital signs, only respiratory rate was not strongly predictive of in-hospital mortality in our study. Earlier research found that well-measured respiratory rate strongly indicates patient risk, but that frequent measurement errors reduce its predictiveness in everyday practice [25-27], which may explain our study findings.

In our study, the most abrupt increases in mortality occurred at very low glucose levels, heart rates, and WBCs. These sudden changes emphasize the need for accurate and precise measurements in these parameter ranges. Separate studies of individual physiological parameters would be needed to characterize specific causes of mortality patterns observed here.

This study has several limitations. One limitation is that this study only examined associations between physiological parameters and in-hospital mortality. In-hospital mortality is also influenced by many other factors, such as the underlying disease or injury that led to admission, preexisting conditions, and treatments administered. If these other factors are not considered and the patient's mortality risk is evaluated solely on the basis of physiological parameter values, then substantial bias or error may occur. Another limitation is typos and other mis-entries of values and/or units, which appear in any large database of hand-entered data, owing to human fallibility. Typos and mis-entries may be especially common among records with extreme values. However, we see no means by which these errors could produce artifactually high mortality rates—the errors consist of mis-entering extreme values for patients whose physiological status is actually more normal or typical, and who therefore do not have rates of death that are as heightened. Therefore, the elevated mortality rates that we report must be due to patients who actually have extreme physiological parameter values. Indeed, the true mortality rate at physiological parameter extremes is only expected to be diluted by the presence of mis-entries, and the actual mortality elevations may therefore be even higher than we have reported. Erroneous values also present a limitation to our analyses of predictive performance because they may misrepresent the patient's condition and thereby degrade predictive performance.

Other limitations include test misclassification, which can occur in large databases for tests with similar names, and the possibility of system and database rules that reject the inclusion of unusual values for some measurements. Given the large number of hospitals contributing to the data (n=207), we are not able to exclude effects of rules like these, which can be hospital-specific. In addition, our analysis was limited to the most deranged value of each physiological parameter in the first 24 hours of admission, but this single value may provide an incomplete picture of the patient's condition. In future research, it may be worth extending analyses to include tem-

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poral trends of physiological parameters. Another limitation is that the definition of the most deranged measurement treats the midpoint of APS scoring categories as the central value [1]. While we followed this definition for consistency with eICU practice, it sometimes resulted in non-typical values being selected as the midpoint (e.g., 38.0 °C instead of the typical body temperature of about 36.8 °C), which may somewhat underestimate parameters' associations with mortality. Lastly, a limitation is that assessments of predictive performance can differ by scoring rule choice [21].

In conclusion, in-hospital mortality rates are greatly elevated for critically ill adults who have extreme values of some physiological parameters, for example reaching at least 50% for patients with very low blood pH, very low or high body temperature, very low glucose level, or very low heart rate measured in the first 24 hours of critical care admission. These relationships are obscured by thresholding and binning of physiological parameters. In clinical practice, vital signs are sometimes treated more casually than laboratory-tested parameters. Yet, our results show vital signs often have better predictiveness for mortality and universally have better availability, supporting opinions that vital signs are currently undervalued.

CONFLICT OF INTEREST

Charles Harding received consulting fees from Exergen, including related to this report. Marybeth Pompei is Senior Vice President of Exergen and has thermometry patents. Dmitriy Burmistrov reports no conflicts of interest. Francesco Pompei is CEO of Exergen and has thermometry patents. Exergen, Corp. is a manufacturer of thermometers. No other potential conflicts of interest relevant to this article were reported.

FUNDING

ACKNOWLEDGMENTS

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AUTHOR CONTRIBUTIONS

Conceptualization: all authors. Data curation: CH. Formal analysis: CH. Funding acquisition: FP. Methodology: CH, DB. Project administration: FP, MP. Visualization: CH. Writing–original draft: CH. Writing–review & editing: all authors.

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Sleep, anxiety, depression, and stress in critically ill patients: a descriptive study in a Portuguese intensive care unit

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Background: Sleep disorders are common among patients admitted to intensive care units (ICUs). This study aimed to assess the perceptions of sleep quality, anxiety, depression, and stress reported by ICU patients and the relationships between these perceptions and patient variables.
Methods: This cross-sectional study used consecutive non-probabilistic sampling to select participants. All patients admitted for more than 72 hours of ICU hospitalization at a Portuguese hospital between March and June 2020 were asked to complete the "Richard Campbell Sleep Questionnaire" and "Anxiety, depression, and Stress Assessment Questionnaire." The resulting data were analyzed using descriptive statistics, Pearson's correlation coefficient, Student t-tests for independent samples, and analysis of variance. The significance level for rejecting the null hypothesis was set to α ≤0.05.
Results: A total of 52 patients admitted to the ICU for at least 72 hours was recruited. The mean age of the participants was 64 years (standard deviation, 14.6); 32 (61.5%) of the participants were male. Approximately 19% had psychiatric disorders. The prevalence of self-reported poor sleep was higher in women (t[50]=2,147, P=0.037) and in participants with psychiatric problems, although this difference was not statistically significant (t[50]=−0.777, P=0.441). Those who reported having sleep disorders before hospitalization had a worse perception of their sleep.
Conclusions: Sleep quality perception was worse in female ICU patients, those with psychiatric disorders, and those with sleep alterations before hospitalization. Implementing early interventions and designing nonpharmacological techniques to improve sleep quality of ICU patients is essential.

Key Words: anxiety; depression; intensive care unit; nursing; sleep; stress

INTRODUCTION

In the intensive care unit (ICU), nurses must continuously assess vital signs, implement and evaluate treatment plans, administer medications, and anticipate and prevent adverse patient outcomes [1]. However, the methods required to care for these patients may limit family par-

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ticipation in decision making, and the patients' psychosocial needs may be neglected [2]. Previous reports have indicated a link between sleep disturbance in critical-care patients and increased incidences of delirium, mortality rates, and hospital stay [3]. Additionally, sleep disturbances have been shown to be associated with short-term symptoms like lethargy, fatigue, irritability, confusion, memory issues, and loss of muscle, which may hinder the recovery process and potentially impact the patient's quality of life in the longer term [4-7].

Sleep deprivation is a common issue faced by patients during hospitalization and ICU care and may be attributed to several factors. The ICU environment may contribute to sleep disruption due to the noise and light and the need for patient care activities, diagnostic procedures, and mechanical ventilation. Sleep quality while in hospital may also be a function of factors related to the patient's health, such as pre-existing sleep disorders, severity and/or acute onset of illness, organ dysfunction, and pain; these factors may also increase stress and anxiety [7,8], which may further disrupt sleep and induce additional stress and anxiety [8].

As sleep disturbance is considered a risk factor for anxiety [9-11], complaints of sleep disturbances are generally regarded as diagnostic criteria for anxiety disorders [12,13]. Furthermore, depression, anxiety, and stress are common in patients who have suffered traumatic brain injury and should be anticipated in critically ill patients [14].

Sleep disturbances among ICU patients are well known but are not currently addressed in a consistent manner. Indeed, in recent years, various strategies have been implemented to promote and improve sleep. However, hospitalized patients often cannot achieve good-quality sleep [15]. Due to the tremendous impact of sleep disturbance on healthcare services, it is crucial to identify patients at higher risk of sleep and mental health disorders after hospitalization to prevent rather than react to possible adverse patient outcomes. Thus, this study aimed to describe and predict the quality of sleep of critically ill patients and to predict possible correlations of sleep disturbances with anxiety, depression, and stress.

MATERIALS AND METHODS

This single-center, cross-sectional, and correlational study analyzed adult patients admitted to a Portuguese ICU between March and June 2020. The hospital's Ethics Committee approved the study (authorization 2020.053, 043-DEFI/045-CE). Informed consent was obtained from all participants after pro-

> ### KEY MESSAGES
> - We suggest routine implementation of sleep quality assessment in intensive care unit patients, including the scales used in this study.
> - It is essential to identify factors that may lead to sleep disturbance in critically ill patients.
> - Therapeutics should be directed at all potential sleep-disturbing factors, optimizing the diurnal and nocturnal environment, and minimizing unnecessary sleep interruptions.

viding them with all necessary information.

The data collection instruments included sociodemographic and clinical characterization and the "Richard Campbell Sleep Questionnaire (RCSQ)" and "Depression, Anxiety and Stress Scale 21 (DASS-21)." The RCSQ is frequently used to assess sleep quality in ICU patients, and many clinical practice guidelines recommend its use [16]. This instrument includes six items (sleep depth, falling asleep, awakenings, return to sleep, sleep quality, and an additional item addressing noise levels) and uses a visual analog scale. The score for each item ranges from 0 (indicating the worst possible sleep) to 100 (indicating the best sleep). A total sleep score is obtained for each patient by summing the individual scores on the five sleep items and dividing the result by five (to obtain a final RCSQ score of 0 to 100). Those within the lowest quartile (scores from 0 to 25) are considered to have the worst sleep, and those within the highest quartile (76 to 100) are deemed to have excellent sleep.

The DASS-21 [17] consists of 42 items evenly distributed across depression, anxiety, and stress subscales [18]. Each scale comprises seven items, each of which is scored with a four-point Likert scale, ranging from 0 ("strongly disagree") to 3 ("strongly agree"). The final result is obtained by summing the scores of the items in each subscale. The cutoff points, indicative of severity, are described in Table 1. This instrument has

Table 1. DASS-21 severety score

Variable	Percentile	Depression	Anxiety	Stress
Normal	0–78	0–4	0–3	0–7
Mild	78–87	5–6	4–5	8–9
Moderate	87–95	7–10	6–7	10–12
Severe	95–98	11–13	8–9	13–16
Extremely severe	98–100	>14	>10	>17

DASS-21: Depression, Anxiety and Stress Scale 21.

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strong evidence for its validity in various areas including bi-factor structural, internal consistency, criterion, and construct validity [19]. The DASS-21 is a high-quality tool used to assess emotional states, although it has inherent limitations with respect to assessing the individual severities of depression, anxiety, and stress [20]. However, given the reliability, validity, and ease of use, the DASS is considered a useful tool for research and clinical settings [21].

Population and Sample

In a consecutive non-probabilistic sampling process, all patients admitted to the ICU who met the following inclusion criteria completed the data collection process: ICU stay longer than 72 hours and able to complete the questionnaire themselves or indicate their answer to the researcher. All patients younger than 18 years, with an ICU stay less than 72 hours, who experienced confusional states (all psychic and autopsychic disorientation states, including delirium), or had been prescribed medication that alters sleep patterns (e.g., sedatives, anxiolytics, and/or analgesics) were excluded.

Data Collection

Firstly, the study's objective and methods were presented to the nursing team. Prior to obtaining informed consent of the participants, the patients who met the inclusion criteria were provided the study objectives and a description of the study design and were asked for their free and informed participation. The principal researcher provided all the necessary information to participants and the authorization to be signed; permission was obtained through a fingerprint (preferably from the index finger of the dominant hand) for those who could not sign. The participants were invited to complete the data collection instruments autonomously. Whenever the patient demonstrated incapacity or a preference for assistance, the researcher filled out the questionnaires according to the indications/answers of the user and revalidated them.

Statistical Analysis

The patients' sociodemographic data were first described using measures of central tendency and dispersion for quantitative variables and absolute and relative frequencies for qualitative variables. The outcomes, including dimensions and total scale, were described using the mean and standard deviation (SD). In all analyses, significance was assessed using an alpha of 0.05. Cronbach's alpha coefficient (a measure of internal consistency), Pearson's correlation coefficient, Student t-test

for independent samples, and the multivariate analysis of variance (ANOVA) test were used for analysis. The normality of the data distributions was analyzed using the Shapiro-Wilk test, and the homogeneity of the variance was analyzed using the Levene test. All data were analyzed using the IBM SPSS version 27.0 (IBM Corp.).

RESULTS

Fifty-two participants completed the survey during the study period (Table 2). The mean age was 64±14.6 years (range, 20–84 years); 32 (61.5%) were men, and 32 were married (62.7%). The median length of stay was 6±3.64 days (range, 3–290 days). About 19% of participants had a history of psychiatric illness.

There were various reasons for ICU admission (Table 3), ranging from gastrointestinal impairment (27.0% of patients) to nervous system impairment (1.9%). The reliability of the questionnaire scales was estimated using Cronbach's alpha coefficient: there was variation observed among the scores of the diverse dimensions between 0.647 (weak but acceptable)

Table 2. Sociodemographic and clinical characterization (n=52)

Variable	Value
Age (yr)	64±15
Sex	
Female	20 (38.5)
Mele	32 (61.5)
Marital status	
Single	8 (15.7)
Married	32 (62.7)
Divorced	5 (9.8)
Widowed	6 (11.8)
Length of stay in ICU (day)	6.0±3.6
Psychiatric history	
No	42 (80.8)
Yes	10 (19.2)
Sleep disturbances (before ICU)	
No	21 (40.4)
Yes	31 (59.6)
Sleep medication (before ICU)	
No	10 (19.6)
Yes	
Sleep medication (during ICU stay)	41 (80.4)
No	11 (22.9)
Yes	37 (77.1)

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

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Table 3. Reason for ICU admission (n=52)

Reason for ICU admission	No. (%)
Gastrointestinal	14 (26.9)
Sepsis	10 (19.2)
Vascular	9 (17.3)
Cardiovascular	5 (9.6)
Multiple trauma	4 (7.7)
Respiratory	3 (5.8)
Endocrine	2 (3.9)
Orthopedic	2 (3.9)
Renal	2 (3.9)
Neurological	1 (1.9)

ICU: intensive care unit.

Table 4. Scale reliability

Scale	α of the dimension	Number of items
RCSQ		
DASS-21	0.837	6
Depression	0.871	7
Anxiety	0.647	7
Stress	0.756	7

RCSQ: Richard Campbell Sleep Questionnaire; DASS-21: Depression, Anxiety and Stress Scale 21.

Table 5. Correlations between depression, anxiety, and stress and sleep

Scale	Depression	Anxiety	Stress
Depression	–	–	–
Anxiety	0.626	–	–
Stress	0.682	0.608	–
RCSQ total	0.452	0.355	0.324

RCSQ: Richard Campbell Sleep Questionnaire.

to 0.871 (good) [22] and is presented in Table 4.

The correlations between anxiety, depression, stress, and sleep quality were statistically significant, positive, and moderate (Table 5). Thus, the higher were the values of anxiety, depression, and stress, the worse was the perception of sleep quality.

With this study, we aimed to test the following hypotheses: H1: women have a worse perception of sleep than men; H2: patients with psychiatric problems have a worse perception of sleep; H3: patients with sleep disorders before hospitalization have worse sleep perception; H4: patients who have experienced sleep disorders in the past may exhibit changes in stress, depression, and anxiety; H5: patients with a history of

Table 6. Relationship between sex and sleep quality

	Female	Male	P-value
Sleep quality	5.2±2.3	3.8±2.1	0.037

Values are presented as mean±standard deviation.

Table 7. Relationship between psychiatric history and sleep quality and sleep quality in ICU

	Psychiatric history		P-value
	Yes	No	
Sleep quality	4.8±3.0	4.2±2.1	0.441
Sleep quality in ICU	5.0±2.4	3.9±2.1	0.073

Values are presented as mean±standard deviation.
ICU: intensive care unit.

Table 8. Relationship between depression, anxiety, and stress and previous sleep changes

	Previous sleep change		P-value
	Yes	No	
Depression	3.95±4.56	4.6±4.70	0.874
Anxiety	5.95±4.11	4.35±2.96	0.110
Stress	6.61±4.66	6.45±3.32	0.880

Values are presented as mean±standard deviation.

any reported psychiatric illness may exhibit changes in stress, depression, and anxiety; Regarding H1, the ICU patients' perception of their sleep quality was significantly worse in women than in men (t(50)=2.147, P=0.037) (Table 6).

Regarding H2, the ICU patients' perception of their sleep quality was worse in those with psychiatric problems (Table 7), although the difference was not significant (t(50)=−0.777, P=0.441). Regarding H3, the ICU patients' perception of their sleep quality was worse in those who reported sleep disturbances prior to hospitalization (Table 7), although the difference was not statistically significant (t(50)=1.831, P=0.073).

Regarding H4, the multivariate ANOVA results indicated that differences in reported stress, depression, or anxiety among the patients who have experienced sleep disorders in the past were not significant (Λ=0.904, F(3.48)=1.708, P=0.178) (Table 8). Regarding H5, a significant positive correlation was found between reported stress, depression, or anxiety and psychiatric history (Table 9). The ICU patients with a history of psychiatric illness more frequently reported more severe depression (7.50 vs. 3.26) and stress (9.50 vs. 5.80).

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Table 9. Relationship between depression, anxiety and stress and psychiatric history

	Psychiatric history		P-value
	Yes	No	
Depression	7.50±5.06	3.26±4.14	0.008
Anxiety	6.30±4.90	4.69±3.11	0.197
Stress	9.50±4.67	5.80±3.35	0.006

Values are presened as mean±standard deviation.

DISCUSSION

In the ICU, numerous stimuli can interfere with the quality of sleep and, consequently, with the outcomes of hospitalized patients [23]. For various reasons, stimuli such as noise are increased in the ICU. On the other hand, beneficial stimuli such as natural light are limited [23,24]. Sleep is an essential biological function and is considered fundamental for good health and quality of life. Sleep quality modulates many body functions, including immune system function, removal of cellular toxins, and control of body temperature, blood pressure, pulse, and hormone production [4,25].

Many ICU patients experience sleep disorders of varying severity related to both intrinsic and extrinsic factors. The ICU staff have an important role in reducing the extrinsic factors that impact sleep quality in the ICU to minimize adverse events. In this study, we assessed the sleep quality of ICU patients and investigated associations between some intrinsic factors and sleep quality in the ICU. The results may allow early identification of ICU patients at higher risk of sleep disturbances during their hospital stay.

The average age of the study participants was 64 years, which is slightly higher than in previous studies [20] but within the reported range. As expected, the participants' sleep quality during hospitalization was reported to be poorer, as age and sleep quality are highly negatively correlated. Although the questionnaire responses indicated that 59.6% of the study participants reported previous sleep disturbances, 80% of the patients also reported use of prescription medications prior to hospitalization, and 77.1% continued to receive their medication during hospitalization.

Critical illness can cause physiological and emotional disorders that can negatively impact sleep quality, regardless of the reason for hospitalization. According to the findings of this study, the participants' mean perception of their sleep quality is below 50%, which could indicate significant changes in sleep

patterns, similar to the findings of other studies [7,24]. However, the perception of sleep quality by the participants, given the average length of stay of six days, with a range of 3 to 290 days, may have been related to extrinsic factors not evaluated in this study, including environment, noise, luminosity, and temperature [7,26,27].

Most ICU patients rate their sleep quality as low [7,24], corroborating the data of this investigation. Low-quality sleep is characterized by a high proportion of stages 1 and 2, fragmented sleep, with circadian rhythm changes; stage 3 and REM sleep may be significantly decreased or absent [28-32]. Reduced sleep quality may increase the length of hospitalization by delaying weaning from ventilation support [33] and increasing the incidence of delirium and, consequently, adverse outcomes [34,35]. Longer length of stay and a weakened immune system due to lack of quality sleep increase the risk of healthcare-associated infection [34,36].

Methods to promote better sleep can include medications, such as benzodiazepines, which may result in changes to cognitive function, increased risk of tolerance and dependence, ventilatory impairment, and adverse effects on sleep patterns [37]. Alternatively, non-pharmacological approaches may be employed, including mental or behavioral interventions, breathing exercises, music therapy, aromatherapy, massage, guided imagery, acupuncture, environmental changes (e.g., synchronization of ICU activities with daylight, noise reduction], social support (e.g., family assistance), and equipment modification [4,24].

However, the use of such strategies may not influence the patient's anxiety and stress and so not improve sleep [9]. The ICU patient typically has abnormally high levels of anxiety and depression [38]. In the present study, the participants' self-reported scores were consistent with moderate depression and stress and mild anxiety, perhaps because the sample demonstrated variability in disease severity and most had short hospital stays. The patient hospitalized in the ICU is subject to numerous stress factors, the most prevalent of which are being thirsty, having invasive devices in the nose and mouth, not being able to communicate, decreased mobility due to invasive and non-invasive devices, not being able to sleep, and loss of autonomy [39]. The data from this study are consistent with the above-noted stressors: the higher were the self-reported scores for anxiety, stress, and depression, the worse was the perception of sleep.

Some studies have reported that sleep duration and quality changes are associated with increased incidence of mental

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health disorders, including depression and anxiety [40]. Conversely, no relationship between previous sleep alterations and stress, depression, or anxiety was found in this study, and there may be other predictive factors of greater importance.

Previous studies have reported that people with mental health issues were much more likely to have a shorter sleep duration and quality [40], as in the present study, in which the perception of sleep quality was worse in ICU patients with psychiatric illnesses. In this study, 80% of the participants patient had no history of mental illness. We also discovered that participants with a history of mental illness had significantly higher scores for self-reported depression and stress, consistent with previous findings [41,42], including those from studies of patients with traumatic brain injury [43], stroke patient [42] oncological disease [44,45], or cardiovascular disease [46-48] and of pregnant [49,50] or postpartum [49,51] women.

In the present study, the perception of sleep was worse in the female participants. A study of healthy adults in Canada found that 55% of women report problems falling asleep, which is higher than men. [52]. In contrast, another study of healthy participants found that women had a significantly longer sleep duration, a lower percentage of stage 1 sleep, and a higher percentage of slow-wave sleep compared to men [53].

Sleep disorders increase the risk of delirium, extend hospital stays, and are associated with prolonged mechanical ventilation. However, evidence-based practices are necessary to manage and improve sleep quality of hospital patients. There is a need to educate hospital nurses about the impact of sleep quality on patient outcomes to better enable them to assess overall condition and to implement appropriate measures to encourage sleep and minimize unfavorable outcomes.

A patient's healthcare plan should include measures to manage sleep quality during hospitalization and strategies to manage sleep disorders and mitigate adverse effects when they occur. By being proactive in these areas, healthcare professionals can better support patients and promote positive outcomes.

There is a need for ICU nurses to employ high-quality, validated tools to monitor and evaluate the sleep quality of their patients and evidence-based strategies to achieve desired results. However, implementing evidence-based methods to assess sleep quality in clinical practice remains a challenge, as does improving the understanding of sleep and sleep disorders among medical staff caring for hospitalized patients. There are several obstacles to promoting sleep in the ICU, including the major trend of reducing sedation for critical patients.

It is essential to exercise caution when interpreting this study's results, as several limitations were involved. The coronavirus disease 2019 (COVID-19) pandemic caused disruptions during the first wave, leading to a reformulation of services and a subsequent reduction in the number of participants. The deteriorating epidemiological situation also necessitated reorganization of the data collection process, further limiting the number of participants.

It is important to consider external variables that may influence an individual's perception of sleep, such as noise, luminosity, and nursing activities. The use of self-reporting instruments, while helpful, may not provide a complete picture of an individual's sleep experience. The assessment of sleep quality is a multidimensional function that includes factors such as total sleep time, awakening, expectations, global perception, nocturnal awakenings, tiredness after waking, day-to-day energy, and other factors. As a result, various tools may be needed to assess different dimensions of sleep.

Further research addressing the quality of sleep among ICU patients is needed. Many aspects of this field have not been adequately studied, including the influence of invasive ventilation and ventilatory modes on a patient's sleep or the impact of inotropic or cardiovascular-active drugs on sleep deprivation. Additional multicenter studies to test interventions and strategies to promote sleep and to minimize alterations of sleep-wake patterns in the ICU, taking into account factors such as disease severity, age, medications, and length of stay, are needed.

When patients are admitted to the ICU, the primary aim of healthcare professionals is to save their lives. However, some life-saving interventions can lead to adverse events and other adverse consequences in the short and medium term, including disruption of sleep. To address this issue, healthcare providers should identify factors that may disturb their patients' sleep and develop intervention plans based on evidence-based strategies.

To improve our understanding of the importance of sleep in ICU patients, we suggest using the scales outlined in this study as a routine practice. Additionally, healthcare providers should receive training on promoting sleep and evaluating its quality.

Data regarding the sleep quality of patents in the ICUs of Portuguese hospitals are limited, and this study provides new insight in this area. The findings support additional exploration of appropriate and practical tools to monitor and to evaluate the quality of sleep in critically ill patients.

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Conceptualization: RDS, ACT, JCS. Methodology: RDS, JCS. Formal analysis: RDS, ACT, JCS. Investigation: RDS, JCS. Visualization: JAS, PM. Writing–Original draft preparation: RDS. Writing–Review and editing: ACT.

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End-of-life care in the intensive care unit: the optimal process of decision to withdrawing life-sustaining treatment based on the Korean medical environment and culture

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Since implementation of the "Act on hospice and palliative care and decisions on life-sustaining treatment (LST) for patients at the end of life" ("LST Decision Act") in Korea in 2018, social interest in the process of facing a "good death" by respecting the patient's right to self-determination of meaningless life support is increasing. Restrictions on LST prevent unnecessary exhaustion of national medical costs and help in the effective distribution of limited medical resources, becoming a common form of death in intensive care units (ICUs). However, the end-of-life (EOL) decision of ICU patients in Korea is still made through subjective judgment by individual doctors in charge of ICU treatment after consultation with mainly their families.

The current study by Kim et al. [1] identified factors affecting the decision to withdraw LST of Korean patients admitted to the ICU. It evaluated how the decision to withdraw LST affects the actual use of medical services by comparing medical costs through retrospective analysis in a tertiary hospital. The authors observed that LST withdrawal decisions are affected by subject age, readmission rate, and disease categories. Notably, families made 86% of LST withdrawal decisions, but the decision rates varied according to disease. The total hospital cost was higher in the LST withdrawal group than in the control group, and there was no significant difference between the groups in the ICU cost. The authors concluded that LST withdrawal should be tailored to the individual characteristics of critically ill patients.

This study was based on the Korean LTS Decision Act, so the results are limited to Korea. However, it can be used as a reference in Asian countries with Confucian culture. There are several points to note when interpreting the results. Most of the ICU patients are those with acutely deteriorated physical conditions, and most had no LST plans at admission, regardless of the type of disease. Unlike incurable diseases such as terminal cancer, acute diseases such as neurological diseases and infections are not easy for patients and their families to consider LST plans before the disease occurs. As EOL patients with chronic diseases are likely to have sufficient consultation with a doctor treating them in the long term, it is likely that families of patients with acute diseases would discuss the LST withdrawal plan with unfamiliar ICU doctors without providing sufficient time for decision. Therefore, the decision making process of LTS withdrawal must be different in the ICU versus non-ICU setting.

The admission route (through the emergency room vs. the general ward) to the ICU should also be considered. If patients are admitted to the ICU during treatment in a general ward, the length of hospitalization is longer than that of those admitted to the ICU through the emergency room, the medical costs are higher, and patients and their families have time to determine the patient's condition in the general ward. Despite the long hospitalization period and high ICU readmission rate, there was no significant difference in ICU medical costs or the lengths of ICU stay between the LST withdrawal group and the control group in this study. Thus, decision-making on LST withdrawal could be more affected by the psychological aspect of the patient's expectation of recovery than the economic aspect.

The mortality rates of the LST withdrawal group and the control group were not statistically different (66% vs. 58%) in this study. One-third of LST withdrawal patients did not die, indicating the possibility of over-diagnosing EOL patients. Decisions of EOL often are affected by the subjective characteristics of ICU doctors and families [2,3]. This finding supports the need for a more precise and tailored LST decision-making process. In addition, the items of LST withdrawn are important to explain the mortality results, although such data were not analyzed in this study.

Consequently, Kim et al. [1] showed factors affecting LST withdrawal decisions in ICU patients and the importance of LST decision plans tailored to the individual characteristics of critically ill patients. Studies considering the cultural background peculiar to Asian countries, where discussion of family deaths is considered a taboo subject [4], are scarce, and the subject of the decision to suspend LST, the method of LST withdrawal, and the location of death differ between South Korea and Western countries [4-6]. Thus, further research to develop the optimal LST decision process based on Korean culture is needed, and the current results will enhance the research interests in EOL care in the ICU in South Korea.

CONFLICT OF INTEREST

Dohhyung Kim is an editorial board member of the journal but 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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Digital tomography in the diagnosis of a posterior pneumothorax in the intensive care unit

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Portable chest radiography is a valuable tool in the intensive care unit. However, the supine position causes superposition of anatomical structures resulting in less reliable detection of certain abnormalities. Recently, a portable digital tomosynthesis (pDTS) prototype with a modified motorized x-ray device was developed. We aimed to compare the diagnostic value of pDTS to standard bedside chest radiography in the diagnosis of a posterior pneumothorax. A modified motorized x-ray device was developed to perform 15 radiographic projections while translating the x-ray tube 25 cm (10 cm ramp up and 15 cm during x-ray exposure) with a total radiation dose of 0.54 mSv. This new technique of pDTS was performed in addition to standard bedside chest x-ray in a patient with a confirmed posterior hydropneumothorax. The images were compared with the standard bedside chest x-ray and computed tomography (CT) images by two experienced radiologists. The posterior hydropneumothorax previously identified with CT was visible on tomosynthesis images but not with standard bedside imaging. Combining the digital tomosynthesis technique with the portable x-ray machine could increase the diagnostic value of bedside chest radiography for the diagnosis of posterior pneumothoraces while avoiding intrahospital transport and limiting radiation exposure compared to CT.

Key Words: bedside chest x-ray; digital tomosynthesis; intensive care unit; posterior pneumothorax

Pneumothorax is a common problem in adult intensive care unit (ICU) patients with a prevalence of 4%–15% in mechanically ventilated patients [1], and up to 50% in patients following chest trauma [2]. Currently, computed tomography (CT)-scan is the gold standard for both the diagnosis and assessing the size of the pneumothorax [3]. Recently, portable digital tomosynthesis (pDTS) prototype with a modified motorized x-ray device was developed [4]. pDTS is a technique where several low dose x-ray images are acquired with a motorized x-ray source which moves relative to a stationary detector. Subsequently, reconstruction algorithms are used to compute coronal section images through the area of interest. This technique may be able to improve the diagnostic value of bedside chest radiography due to its ability to distinguish overlapping anatomical structures. Chest digital tomosynthesis is a technique

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already available on a wall mounted flat panel or x-ray table, however, there is currently no pDTS available on the market [5].

We describe a case that highlights its potential in critically ill patients. This study was approved by our local Institutional Review Board (IRB No. 143202043138) and all patients or designated proxies provided written informed consent. Authors with no ties to Agfa Radiology Solutions had unrestricted control over the data during the study.

CASE REPORT

A 62-year-old man was admitted to the ICU following respiratory failure due to coronavirus disease 2019 (COVID-19) pneumonia. His stay was further complicated by several ventilator acquired pneumonias and the requirement of venovenous extracorporeal membrane oxygenation. Due to respiratory deterioration on day 41 of hospital admission a CT thorax was performed which initially showed subcutaneous

emphysema and a pneumomediastinum without evidence of a pneumothorax (Figure 1A). Respectively, 2 and 7 days later, a pneumothorax at the left apex as well as at the right apex was visualized on a standard bedside chest x-ray for which a chest drain was placed (Figure 1B-E). Twelve days after the initial CT scan a new CT scan was performed to re-evaluate the extent of the pneumothoraces after drain insertion. This showed an additional posterobasal hydropneumothorax on the right which was not visible on standard bedside chest x-ray (Figure 1F). Subsequently, an additional chest drain was inserted. Analysis of the fluid suggested an empyema for which antibiotics were initiated.

After the acute phase, on day 151 since admission, a portable DTS acquisition was performed in addition to the standard bed-side chest radiography with a prototype device (Agfa Radiology Solutions). Fifteen x-ray projections were made while translating the x-ray tube 25 cm with a synchronized motorized system (10 cm ramp up and 15 cm during x-ray exposure)
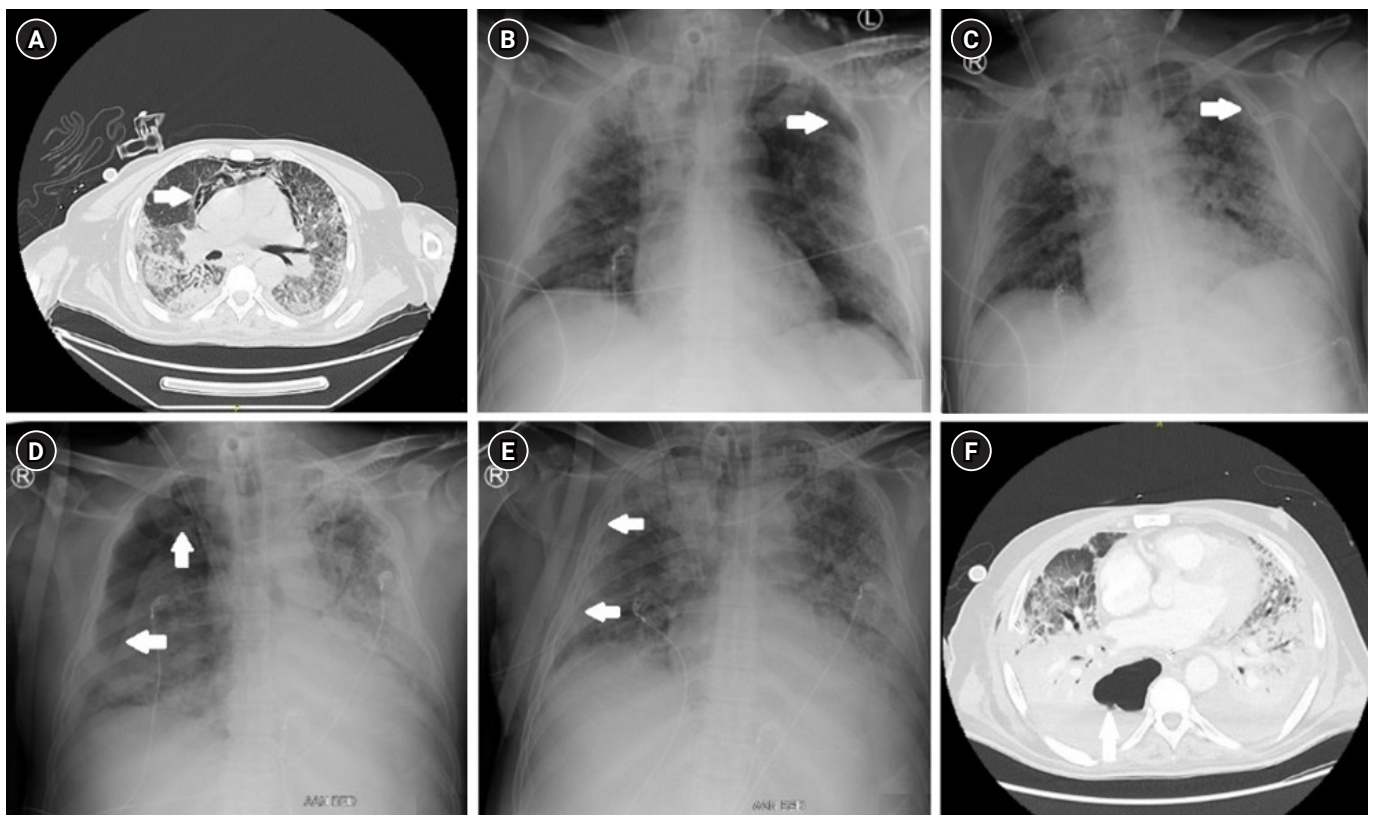
Figure 1. (A) Computed tomography (CT) thorax on day 41 of admission showing subcutaneous emphysema and a pneumomediastinum (arrow). (B) Standard bedside chest x-ray. Arrow, pneumothorax at the left apex. (C) Standard bedside chest x-ray after drain insertion (left). Arrow, resolution of the pneumothorax at the left apex with drain *in situ*. (D) Standard bedside chest x-ray: pneumothorax at the right apex (arrow). (E) Standard bedside chest x-ray after drain insertion (right). Arrow, resolution of the pneumothorax at the right apex with drain *in situ*. (F) CT thorax 12 days after the initial CT thorax illustrating a postero-basal hydropneumothorax on the right.

with a total acquisition time of about 3.2 seconds. Subsequently images were reconstructed using the simultaneous iterative reconstruction technique (SIRT) algorithm using 25 iterations. The estimated effective radiation dose of the pDTS acquisition was 0.54 mSv (in comparison to a typical radiation dose of 0,1 mSv in standard chest radiography, and 6.2 mSv for chest CT) [6]. A radiological comparison was made between the pDTS images and the standard bedside chest x-ray by two experienced chest radiologists. A posterior (hydro)pneumothorax which had previously been identified with CT thorax appeared while scrolling through the tomosynthesis images (Figure 2A) but was not visible on the standard bedside radiography imaging (Figure 2B).

DISCUSSION

Portable chest radiography is a valuable tool frequently used in ICU, especially when the condition of the patient deteriorates. However, the supine position anteroposterior exam in a bedbound ICU patient with suboptimal positioning causes superposition of anatomical structures resulting in less reliable detection of certain abnormalities, such as a pneumothorax [7]. The presented case describes the potential diagnostic benefit of the pDTS technique compared to the standard portable chest x-ray. The combination of digital tomosynthesis technique with the already widely used portable x-ray machine could increase the diagnostic value of portable chest radiography in ICU as is presented in this case.

Ultrasound is a useful bedside radiological technique which, in the diagnosis of pneumothorax, has been shown to have a higher sensitivity and similar specificity compared to standard chest x-ray. However, the accuracy of ultrasound in the diagnosis of pneumothorax is operator-dependent and requires a critical care ultrasound-trained physician [8].

CT scan is currently the gold standard for the diagnosis and assessing the size of a pneumothorax. CT scan still has an advantage compared to pDTS with regards to assessing the size of a pneumothorax, as further studies are still required to assess the calibration of pDTS as well as the characterization of error margins of measurements. However, there are two major disadvantages of CT scan compared to pDTS. First, in order to perform a CT scan, the patient requires an intrahospital transport. This transport is associated with numerous risks and complications (up to 60%) [9]. Portable CT scanners, if available, are expensive and would require logistical adaptations to be utilized in the ICU setting. pDTS can be readily performed bedside, eliminating the risks associated with intrahospital transport of the patient, in turn also decreasing the risk of virus transmission in the current COVID-19 pandemic.

Secondly, pDTS is associated with a much lower radiation dose (0.54 mSv) than a chest CT scan (6.2 mSv) [6]. ICU patients have an important radiation exposure due to repetitive thorax radiography and CT scans [10]. Following the ALARA principle (as low as reasonably achievable), it is appropriate to limit radiation exposure in ICU patients. Using pDTS would reduce the cumulative radiation exposure if CT scan could be
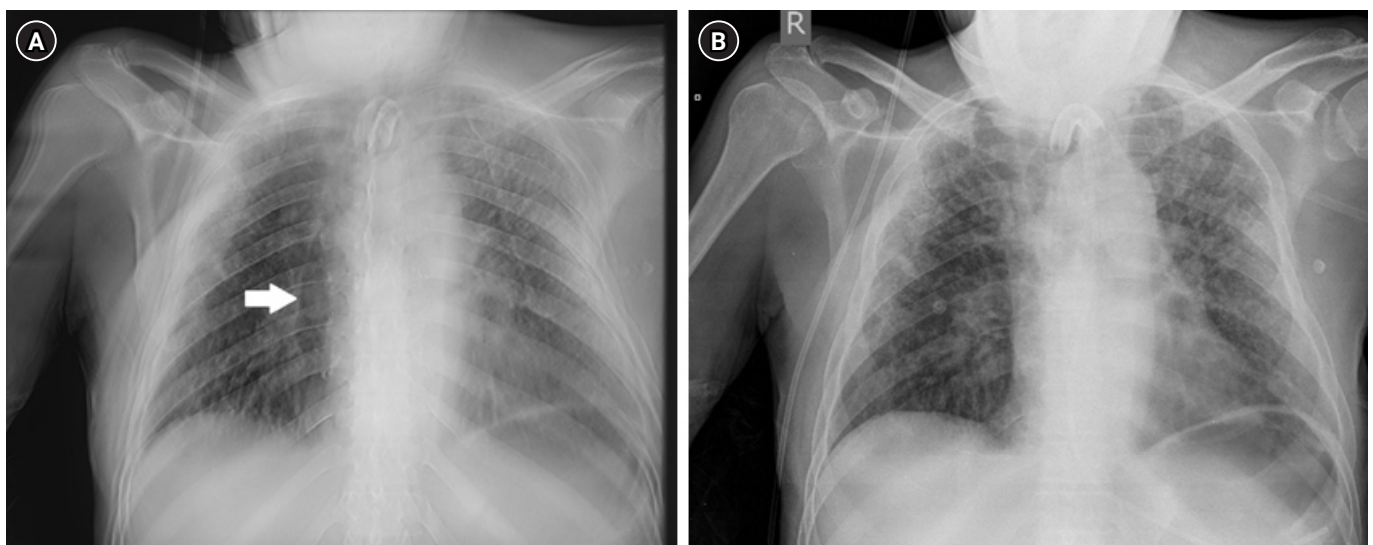
Figure 2. (A) Bedside portable digital tomosynthesis image showing a posterior pneumothorax on the right thorax (arrow). (B) Standard bedside chest radiography: no pneumothorax visible.

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avoided.

Although the technique seems promising, further research is needed. In the ICU setting imaging is subject to respiration motion artefact. The application of a motion correction algorithm could therefore further improve image quality, however, this is subject to further research. Furthermore, it is necessary to evaluate the sensitivity and specificity of this new technology. In order to do so, the comparison with CT scan, classic chest radiography and ultrasonography must be made in critically ill patients to assess the place of pDTS for the diagnosis of pneumothorax in the ICU setting.

CONFLICT OF INTEREST

FUNDING

ACKNOWLEDGMENTS

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Could fever dreams influence sleep in intensive care units?

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Dear Editor:

Ahn et al. [1] describes multiple factors that may influence sleep quality in intensive care units (ICUs). Another phenomenon that may interfere with the sleep of ICU patients is nightmares and distressing dreams [2]. While there are many mechanisms that may contribute to such dreams, one possible contributing factor is "fever dreams," a topic that is relatively unexplored. "Fever dreams," which are commonly referenced in songs, books, artwork, and films, refer to the experience of vivid, bizarre dreams during a febrile episode. Plausible mechanisms for fever dreams include disrupted rapid eye movement (REM) sleep time, and the continuity hypothesis, which describes dreams to reflect waking life thoughts and experiences [3]. However, scientific evidence for this phenomenon remains less abundant than popular culture references. Therefore, a review was conducted to characterize dreams that occur during a fever ("fever dreams"), in particular with respect to content (e.g., realism, bizarreness, emotional valence, temperature-related content, and health-related content) and how this content differs from regular dreams.

The databases PubMed, PsycINFO, and Embase were searched for studies pertaining to fever dreams (Supplementary Materials 1 and 2 for details). Titles and abstracts underwent screening prior to full-text review for eligibility determination. All search results were reviewed in duplicate (by ST, JSN, and SB) for eligibility determination, with disagreement resolved through consensus or discussion with a third reviewer. To be included, a study was required to fulfill the following criteria: (1) English-language; (2) primary peer-reviewed research articles (excluding abstracts, reviews, and individual case reports); (3) include human participants; (4) describe the characteristics of dreams with fever (dream content or frequency) and dreams in a non-fever comparator group; and (5) be available in full-text. Data were extracted using a standardized format. Joanna Briggs Institute checklists appropriate for study design were used to perform quality analysis. Quality analysis was undertaken in duplicate.

Initial searches returned 654 results. There were three studies that fulfilled the inclusion criteria (Figure 1) [3-5]. The included studies were of moderate-to-low quality (Supplementary Material 3). The details of the included studies are summarized in Supplementary Material 4.

Two studies presented information on fever dream content. In the 2020 study by Schredl

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654 Publications identified
222 PubMed
370 Embase
62 PsycINFO

645 Publications excluded after review of title/abstract
112 Duplicates
18 Not published in English
118 Not primary research article
106 No human participants
291 No fever dreams

9 Full-text articles reviewed

6 Publications excluded after review of title/abstract
0 Not published in English
2 Not primary research article
0 No human participants
4 No fever dreams
0 No full-text

3 Articles included in review

Figure 1. Study selection.

and Erlacher [3], 152 individuals were surveyed online (with the link distributed via a website for people interested in dreaming, namely lucid dreaming). This cohort was then compared to a matched control cohort without fever. Acknowledging the limitations of the study design, significant differences were observed in dream content between the two cohorts. In particular, fever dreams were more likely to be bizarre, have negative emotional valence, involve engagement with fewer people, have more health-related topics, and have more thermal-related content.

The only other study that described fever dream content was also conducted by the Schredl research group in 2016. In this study hardcopy surveys were distributed to psychology students and patients in general practitioner waiting rooms [4]. A sample size of 62 individuals was obtained, of whom 45 had fever dreams. The participants were matched to a control cohort. In this study, fever dreams were described as being significantly more bizarre. It was also reported that fever dreams had a greater intensity than the dreams of the control group, although the statistical significance of this finding was not reported.

Two studies also reported fever dream frequency. In the Schredl and Erlacher's 2020 online survey [3] (n = 152), 15.79% of respondents had dreams every day they had a fever, 19.74% more than half the days they had a fever, 19.08% approximately half the days, 24.34% less than half, and 21.05% never. The frequency of dreams in the same categories for the control group

was not presented. In Karacan et al. [5], a group of 11 male medical students had aspects of their sleep evaluated with and without an intravenous injection of pyrogen prior to sleep onset (either a steroid metabolite or a Salmonella-derived endotoxin). This was the only study in which objective fevers were observed (highest 38.9 °C). In this study, participants were less likely to dream on nights with fever (17%) compared to baseline nights without fever (79%) or on post-febrile recovery nights (80%) ($P<0.05$). This effect was observed in a setting of concomitant increases in sleep disruption and reduced REM sleep.

Available evidence, while limited, suggests that fever dreams may be an entity characterized by more intense, bizarre, and negative dreams [3-5]. Data regarding fever dreams indicate that some members of the population may experience them relatively frequently. Therefore, for patients admitted to ICU with fever, such dreams could theoretically influence their experience and sleep. There are numerous other factors that may also influence dreams in this context, including psychosocial factors, medications, and underlying medical conditions (Supplementary Material 5).

Dreams that are intense, bizarre, and laden with negative emotions can lead to the formation of delusional memories in ICU patients [6]. These delusional memories are associated with significantly poorer health-related quality of life measures, and a higher likelihood of long-lasting psychological effects such as anxiety, depression, and posttraumatic stress disorder [6]. Therefore, it is imperative for post-ICU care to incorporate appropriate psychological treatment in patients who experience fever dreams [7].

This review is based on the evidence available in peer-reviewed literature; therefore, the findings may be influenced by publication bias. The exclusion of non-English studies may have also prevented the detection of potentially useful research, particularly given the potential for psycho-sociocultural influences on dreams. Future studies in this area should seek to control for comorbidities and medications known to influence dreams. Prior to controlling for comorbidities and medications, surveying hospital and ICU inpatients, among whom temperatures are already routinely recorded may provide further insights.

In conclusion, as described, there are multiple factors that may affect sleep in the ICU [1], including distressing dreams [2]. Dreams in the setting of fever could be one such factor contributing to the ICU patient experience. Acknowledging the limited data available on this topic, the available findings sug-

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gest that dreams during periods of fever may be more intense, bizarre, and negative than dreams at other times.

CONFLICT OF INTEREST

FUNDING

ACKNOWLEDGMENTS

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SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4266/acc.2023.01074.

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Corrigendum to: Development of a deep learning model for predicting critical events in a pediatric intensive care unit

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In the article entitled "Development of a deep learning model for predicting critical events in a pediatric intensive care unit," the IRB number was incorrectly presented: No. H-1408-101-605 should read "H-2106-197-1231."

Corrigendum

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Any investigations involving humans and animals should be approved by the Institutional Review Board and Animal Care Committee, respectively, of the institution at which the study took place. ACC will not consider any studies involving humans or animals without appropriate approval. Informed consent should be obtained, unless waived by the institutional review board, from patients who participated in clinical investigations. Human subjects' names, initials, hospital, dates of birth or other personal or identifying information should not be used. Images of human subjects should not be used unless the information is essential for scientific purposes and explicit permission has been given as part of the consent. Even where consent has been given, identifying details should be omitted if they are not essential. If identifying characteristics are altered to protect anonymity, authors should provide assurances that such alterations do not distort scientific meaning. Formal consents are not required for the use of entirely anonymized images from which the individual cannot be identified- for example, x-rays, ultrasound images, pathology slides or laparoscopic images, provided that these do not contain any identifying marks and are not accompanied by text that might identify the individual concerned. If consent has not been obtained, it is generally not sufficient to anonymize a photograph simply by using eye bars or blurring the face of the individual concerned. If experiments involve animals, the research should be based on national or institutional guidelines for animal care and use. Original articles submitted to ACC that address any investigation involving humans and animals should include a description about whether the study was conducted with approval of the institutional review board (with or without patient informed consent) and animal care committee, respectively, of the institution at which the study was conducted. ACC may also request an approval by the institutional review board or animal care committee for other types of articles when necessary. The content of each article is the responsibility of the authors and not of ACC.

2. Registration of Clinical Trial Research

Any research that deals with a clinical trial should be registered with a primary national clinical trial registration site such as https://cris.nih.go.kr/cris/index.jsp, or other primary national registry sites accredited by the World Health Organization (http://www.who.int/ictrp/network/primary/en/) or clinicaltrial.gov (http://clinicaltrials.gov/), a service of the United States National Institutes of Health.

3. Conflicts of Interest

A conflict of interest exists when an author (or the author's institution), reviewer, or editor has financial or personal relationships that inappropriately influence (bias) their actions (such relationships are also known as dual commitments, competing interests, or competing loyalties). These relationships vary from being negligible to having great potential for influencing judgment. Not all relationships represent true conflicts of interest. On the other hand, the potential for a conflict of interest can exist regardless of whether an individual believes that the relationship affects their scientific judgment. Financial relationships (such as employment, consultancies, stock ownership, honoraria, and paid expert testimony) are the most easily identifiable conflicts of interest and the most likely to undermine the credibility of the Journal, the authors, and science itself. However, conflicts can occur for other reasons, such as personal relationships, academic competition, and intellectual passion (http://www.icmje.org/conflicts-of-interest/). If there are any conflicts of interest, authors should disclose them in the manuscript. The conflicts of interest may occur during the research process; however, the important point is the disclosure itself. Disclosure allows the editors, reviewers, and readers to approach the manuscript with an understanding of the situation under which the research work was processed.

4. Authorship

Authorship credit should be based on (1) substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet these four conditions. If the number of authors is greater than six, a list should be included of each author's role for the submitted paper. Policies on research and publication ethics that are not stated in the Instructions can be found in the Guidelines on Good Publication (http://publicationethics.org/) or Good Publication Practice Guidelines for Medical Journals (http://kamje.or.kr/).

5. Originality and Duplicate Publication

Manuscripts that are under review or have been published by other journals will not be accepted for publication in ACC, and articles published in this journal are not allowed to be reproduced, in whole or in part, in any type of publication without the permission of the Editorial Board. Figures and tables can be used freely if the original source is verified according to the Creative Commons Non-Commercial License. It is mandatory that all authors resolve any copyright issues when citing a figure or table from a different journal that is not open-access. Regarding duplicate publication, plagiarism, and other problems related to publication ethics, the "Good Publication Practice Guidelines for Medical Journals" (https://www.kcse.org/resources/, http://publicationethics.org, https://www.kamje.or.kr/board/lists?b_name=bo_publication) should be followed.

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It is possible to republish a manuscript if it satisfies the condition of secondary publication of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals by International Committee of Medical Journal Editors, available from: http://www.icmje.org/ as follows:

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The paper for secondary publication is intended for a different group of readers; therefore, an abbreviated version could be sufficient. The secondary version faithfully reflects the data

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When the Journal faces suspected cases of research and publication misconduct such as redundant (duplicate) publication, plagiarism, fraudulent or fabricated data, changes in authorship, undisclosed conflicts of interest, ethical problems with a submitted manuscript, a reviewer who has appropriated an author's idea or data, or complaints against editors, the resolution process will follow the flowchart provided by the Committee on Publication Ethics (http://publicationethics.org/resources/flowcharts). Discussions and decisions on suspected cases are conducted by the Editorial Board.

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The Editorial Board will continuously work to monitor/safeguard publication ethics: guidelines for retracting articles; maintenance of the integrity of the academic record; preclusion of business needs from compromising intellectual and ethical standards; publishing corrections, clarifications, retractions, and apologies when needed; and ensuring that there is no plagiarism and no fraudulent data in publications. Editors maintain the following responsibilities: the responsibility and authority to reject/accept articles; no conflicts of interest with respect to articles they reject/accept; the acceptance of a paper when reasonably certain; promoting the publication of corrections or retractions when errors are found; and the preservation of the anonymity of reviewers.

MANUSCRIPT PREPARATION

Manuscripts should be written in English. Medical terminology should conform to the most recent edition of Dorland's Illustrated Medical Dictionary.

1. General Principles
1) Word processors and format of manuscript
Manuscripts should be submitted in the file format of Microsoft Word 2003 or higher. Manuscripts should be typed on an A4-sized document, be double-spaced, and use a font size of 12 point with margins of 2 cm on each side and 3 cm for the upper and lower ends. Double spaces should be left between the lines.

2) Abbreviation of terminology
Abbreviations should be avoided as much as possible. One word should not be expressed through an abbreviation, although more than two words may be expressed through an abbreviation. The full term for which the abbreviation stands should be used at its first occurrence in the text. Abbreviations should not be present in the title. Common abbreviations, however, may be used, such as DNA.

3) Units
The use of International Standardized (SI) units is encouraged. These are available at https://physics.nist.gov/cuu/Units/index.html or https://physics.nist.gov/cuu/pdf/sp811.pdf.

4) Machine and equipment
When the use of reagents or devices is reported in the text, the name of the manufacturer should be indicated.
   Ex) Iohexol (Omnipaque, GE HealthCare)

5) Statistics
Statistical methods must be described and the program used for data analysis, and its source, should be stated.

6) Arrangement of manuscript
The article should be organized in the order of Title page, Abstract, Introduction, Materials and Methods, Results, Discussion, Conflict of Interest, Acknowledgments, Open Researcher and Contributor ID (ORCID), Authors' contributions, References, Table, Figure, and Figure Legends.
The title of each new section should begin on a new page. Number pages consecutively, beginning with the abstract page. Page numbers should be placed at the middle of the bottom of each page.

7) Reporting guidelines for specific study designs
Research reports frequently omit important information. As such, reporting guidelines have been developed for a number of study designs that some journals may ask authors to follow. Authors are encouraged to also consult the reporting guidelines relevant to their specific research design. A good source for reporting guidelines is the EQUATOR Network (http://www.equator-network.org/home/) and the United States National Institutes of Health/National Library of Medicine (http://

www.nlm.nih.gov/services/research_report_guide.html).

2. Organization of Manuscript – Original Article

1) Title page

Title: The title should be concise and precise. The first letters of nouns, adjectives, verbs, and adverbs in titles should be capitalized. The title should use generic drug names, not brand names.

Authors and affiliations: First, middle, and last names should be included for each author. If the author is affiliated with multiple departments, this should be included in a footnote by their name. If authors are affiliated with multiple departments and hospitals, affiliations should be arranged in the order of authors and demarcated with a number.

Running head: A running head of no more than 50 characters including letters and spaces should be included in English. If the included running head is inappropriate, the Editorial Board may revise it.

Corresponding author: The corresponding author's name, postal code, address, telephone number, fax number, e-mail address should be included.

2) Abstract

All manuscripts should contain a structured abstract. Abstracts should be no more than 250 words in length and must have the following headings: Background, Methods, Results, and Conclusions. The quotation of references must not be included in the abstract. A maximum of 6 keywords should be listed, immediately after the abstract, in alphabetical order. Each key word should be separated by a semicolon (;). The authors should use MeSH (Medical Subject Heading) terms in their key words (https://meshb.nlm.nih.gov/).

   Ex) Key Words: carbon dioxide; cerebral vessels; oxygen; spinal analgesia

   Ex) Key Words: 2-adrenoceptor agonist; GABA; oxygen

3) Key Messages

A list of 2 or 3 key messages is required. This provides a quick structured synopsis of the important findings of your manuscript and their meaning. This section is limited to 50-100 words or less.

4) Introduction

The introduction should address the purpose of the article concisely and include background reports that are relevant to the purpose of the paper.

5) Materials and Methods

When reporting experiments with human or animal subjects, the authors should indicate whether they received approval from the IRB for the study, and agreement from the patients. When reporting experiments with animal subjects, the authors should indicate whether the handling of animals was supervised by the Institutional Board for the Care and Use of Laboratory Animals. Sufficient details need to be addressed in the methodology section of an experimental study so that it can be further replicated by others. Ensure correct use of the terms sex (when reporting biological factors) and gender (identity, psychosocial, or cultural factors), and, unless inappropriate, report the sex and/or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex and gender. If the study involved an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., prostate cancer). Authors should also define how they determined race or ethnicity and justify their relevance.

6) Results

Results should be presented in a logical sequence in the text, tables, and illustrations, giving the main or most important findings first. Do not repeat all of the data in the tables or illustrations in the text; emphasize or summarize only the most important observations.

7) Discussion

Discussion should emphasize the new and important aspects of the study, including the conclusions. Do not repeat the results in detail or other information that is included in the Introduction or Results sections. Describe the conclusions according to the purpose of the study but avoid unqualified statements that are not adequately supported by the data. Conclusions may be stated briefly in the last paragraph of the Discussion section.

8) Conflict of Interest

If there are any conflicts of interest, authors should disclose them in the manuscript. Disclosures allow editors, reviewers, and readers to approach the manuscript with an understanding of the situation and background of the completed research. If there are no conflicts of interest, authors should include following sentence: "No potential conflict of interest relevant to this article was reported."

9) Funding

Funding for the research should be provided here. Providing a FundRef ID is suggested, including the name of the funding agency, the country, and if available, the number of the grant provided by the funding agency. If the funding agency does not have a FundRef ID, please ask the agency to contact the FundRef registry (e-mail: fundref.registry@crossref.org). A detailed description of the FundRef policy can be found at http://www.crossref.org/fundref/.

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Persons or institutes that contributed to the papers but whose contribution was not significant enough to be co-authors may be introduced at the end (between Discussion and References).

11) ORCID (Open Researcher and Contributor ID)

All authors are recommended to provide an ORCID. To obtain an ORCID, authors should register at the ORCID website: https://orcid.org. Registration is free for all researchers.

12) Authors' contributions

The work authors have conducted for the study should be described in this section. To qualify for authorship, all contributors must meet at least one of the seven core contributions by CRediT (conceptualization, methodology, software, validation, formal analysis, investigation, data curation), as well as at least one of the writing contributions (original draft preparation, review, and editing). Authors may also satisfy the other contributions; however, these alone will not qualify them for authorship. Contributions will be published with the final article and they should accurately reflect contributions to the work. The submitting author is responsible for completing this information at submission, and it is expected that all authors will have reviewed, discussed, and agreed to their individual contributions ahead of this time. The information concerning sources of author contributions should be included in this section at the submission of the final version of the manuscript (at the first submission, this information should be included in the title page).

Examples of authors' contributions are as follows:

Conceptualization: MHC. Data curation: JH. Formal analysis: YIA. Funding acquisition: MHC. Methodology: MHC, JH, YIA. Project administration: YIA. Visualization: MHC, JH, YIA. Writing – original draft: JH, YIA. Writing – review & editing: MHC, JH, YIA.

13) References

References should be obviously related to the document and cited in sequential order in the text. The description of the Reference section is provided below. The References follow the NLM Style Guide for Authors, Editors, and Publishers (http://www.nlm.nih.gov/citingmedicine) if not specified below.

References should be identified in text with full-size Arabic numerals on the line and in square brackets [ ]. All of the references should be stated in English, including author, title, and name of journal. If necessary, the reviewers and the Editorial Board may request original documents of the references. In the Reference section, journals should be abbreviated according to the style used in the list of journals indexed in the NLM Journal Catalog (http://www.ncbi.nlm.nih.gov/nlmcatalog/journals). Journal titles that are not listed in the Catalog should follow the ISO abbreviation as described in "ISO 4:1997 Information and documentation--Rules for the abbreviation of title words and titles of publications" (http://www.iso.org/iso/home/store/catalogue_tc/catalogue_detail.htm?csnumber=3569).

Up to six authors may be listed. If a reference has more than six authors, only list the first six authors with "et al." Provide the start and end page numbers of the cited reference.

Examples of reference style

A. Journal Article

Authors. Article title. Journal title Published year;Volume: Start-End page.

1. Lee DH, Kim EY, Seo GJ, Suh HJ, Huh JW, Hong SB, et al. Global and regional ventilation during high flow nasal cannula in patients with hypoxia. Acute Crit Care 2018;33:7-15.
2. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, et al. The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994;149:818-24.
3. Orengo CA, Bray JE, Hubbard T, LoConte L, Sillitoe I. Analysis and assessment of abinitio three-dimensional prediction, secondary structure, and contacts prediction. Proteins 1999;43(Suppl 3):149-70.

B. Book

Authors. Book title. Edition*. Publisher; Published year.
*Mark edition if it is beyond the 2nd edition.

4. Nuwer MR. Evoked potential monitoring in the operating room. 2nd ed. Raven Press; 1986.

C. Book Chapter
Authors of chapter. Title of chapter. In: Editors of book, editor(s). Title of book. Edition. Publisher; Published year. p. Start-End page.

5. Blitt C. Monitoring the anesthetized patient. In: Barash PG, Cullen BF, Stoelting RK, editors. Clinical anesthesia. 3rd ed. Lippincott-Raven; 1997. p. 563-85.

D. Electronic Format
· Electronic publication before print

6. Lee OJ, Cho YH, Hwang J, Yoon I, Kim YH, Cho J. Long-term extracorporeal membrane oxygenation after severe blunt traumatic lung injury in a child. Acute Crit Care 2017 Feb 10 [Epub]. https://doi.org/10.4266/acc.2016.00472

· Website

7. Sage Terapeutics. A study with SAGE-547 for superrefractory status epilepticus [Internet]. U.S. National Library of Medicine; 2000 [cited 2016 Nov 12]. Available from: https://clinicaltrials.gov/ct2/show/NCT02477618?term=NCT02477618&rank=1

14) Tables
Each table should be consecutively typed or printed on a separate sheet of paper in the order of citation in the text. Supply a brief title at the top of the table. The titles of tables start with "Table 1." Footnotes should be provided consecutively in order of the information, statistics, and abbreviations. Footnoted information should be referenced using small letters (ex; a), b)) in alphabetical order.

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ACC publishes in full color and encourages authors to use color to increase the clarity of figures. Authors must submit figures and illustrations as electronic files. Images must be provided as TIFF files. JPEG is also acceptable when it is the original format. Each figure must be of good quality, higher than 300 dpi resolution with good contrast and sharpness. Figures must be sized to 4 inches. If possible, submit the original file without any modifications.

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All figures and photos should be described in the text separately. The description order must be the same as in the footnotes in tables and should be in recognizable sentences. In microscopic pictures, staining methods and magnification ratio should be indicated.

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The Editorial Board requests review articles of particular titles and text. Author can describe text that is not itemized. Review articles should include unstructured abstracts equal to or less than 250 words in English. Key words should follow ordinary processes. The length of the text excluding references, tables, and figures should not exceed 5,000 words.

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Letters to the Editor should include brief constructive comments that concern a published article; a short, free-standing opinion; or a short, interesting case. Letters to the Editor should be submitted no more than 6 months after the relevant paper has been published. The main text should not exceed 1,000 words and the total number of references is limited to 5. Letters may be edited by the Editorial Board, and if necessary, responses from the author of the relevant paper may be provided. The responses should have the same format of Letters to Editor.

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The images section must be of high scientific quality and value and provide didactic and self-explanatory lessons. Images must be unique and adhere to ethical standards with patient/relative approval when appropriate and ensure protection of patient identity and privacy.

The total text should not exceed 200 words. A maximum of five authors is permitted. Up to 5 references are allowed. No abstract is required.

The legend for the image should concisely present relevant clinical information, including a short description of the patient's history, relevant physical and laboratory findings, clinical course, response to treatment (if any), and condition at last follow-up. All labeled structures in the image should be

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1) Screening process will conducted after submission. If the manuscript does not fit the aims and scope of the Journal or does not adhere to the Instructions to authors, it may be re-

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2) Before reviewing, all submitted manuscripts are inspected by Similarity Check powered by iThenticate (https://www.crossref.org/services/similarity-check/), a plagiarism-screening tool. If a too high a degree of similarity score is found, the Editorial Board will do a more profound content screening.
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2. Peer Review Process
1) Submitted manuscripts will be reviewed by 2 or more experts in the corresponding field. The Editorial Board may request authors to revise the manuscripts according to the reviewer's opinion. After revising the manuscript, the author should upload the revised files with a reply to each item of the reviewer's opinion. The revised part should be marked as red font with underline.
2) The author's revisions should be completed within 30 days after the request. If it is not received by the due date, the Editorial Board will not consider it for publication again.
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4) The Editorial Board may request authors to correct English to reach a certain standard and authors should accept the request.
5) The Editorial Board will make a final decision on the approval of the submitted manuscript for publication and can request any further corrections, revisions, and deletions of the article text if necessary. Statistical editing is also performed if the data requires professional statistical review by a statistician.

3. Process after Acceptance
If the manuscript is finally accepted, the proofreading will be sent to the corresponding author after professional manuscript editing and/or English proofreading. Proofreading should be performed again for any misspellings or errors by the authors. Before final proofreading, the manuscript may appear at the journal homepage as an epub ahead of print with a unique

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ACC accepts the ICMJE recommendations for data sharing statement policy (http://icmje.org/icmje-recommendations.pdf). All manuscripts reporting clinical trial results are recommended to submit a data sharing statement following the ICMJE guidelines from 1 January 2019. Authors may refer to the editorial, "Data Sharing Statements for Clinical Trials: A Requirement of the International Committee of Medical Journal Editors," in JKMS Vol. 32, No. 7:1051-1053 (http://crossmark.crossref.org/dialog/?doi=10.3346/jkms.2017.32.7.1051&domain=pdf&date_stamp=2017-06-05).

Check List for Authors

A. Confirmation by authors

Items	Check points
Originality	☐ Confirm that neither the manuscript submitted nor any part of it has been published or is being considered for publication elsewhere.
Research ethics	☐ Confirm that your study complies with the ethical guidelines for research and publication described in Good Publication Guidelines for Medical Journals and Guidelines on Good Publication.
Disclosure	☐ Disclose any commercial associations with specific products or financial support from any company.
Funding	☐ Acknowledge any research funds, sponsorships, or grants.
Thesis	☐ State that your article is a thesis for a degree such a Master's or PhD degree, if applicable.
Presentation	☐ If your article was presented in a national or international meeting, describe this.
English proofreading	☐ State whether your article was revised or edited by a professional English proofreader.

B. Structure of article

Items	Check points
Sequence	☐ Title page, abstract and keywords, main text, conflict of interest, (acknowledgments), references, table, table legends, figure legends
Title page	☐ Title: The title should be concise and precise. The first letters of nouns, adjectives, verbs, and adverbs in titles should be capitalized. The title should use generic drug names, not brand names.
	☐ Authors and affiliations: First, middle, and last names should be included for each author. If the author is affiliated with multiple departments, this should be included in a footnote by their name. If authors are affiliated with multiple departments and hospitals, affiliations should be arranged in the order of authors and demarcated with a number.
	☐ Running head: A running head of no more than 50 characters including letters and spaces should be included in English. If the included running head is inappropriate, the Editorial Board may revise it.
	☐ Corresponding author: The corresponding author's name, postal code, address, telephone number, fax number, e-mail address should be included.
Manuscript	☐ All manuscripts are typed in 12-point font size, double-spaced, and saved as an MS Word file.
	☐ Any text that identifies me as the author or my affiliation is deleted from the title page and manuscript text.
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	☐ The running head is less than 50 characters.
	Original Article
	☐ Manuscripts include an Abstract, Key Words, Introduction, Materials and Methods, Results, Discussion, Conflict of Interest, (Acknowledgments), References, Table(s), and Figure(s) in the order listed.
	Letters to the Editor
	☐ Letters to the Editor should include brief constructive comments that concern a published article; a short, free-standing opinion; or a short, interesting case.

Items	Check points
Abstract	☐ Key words (up to 6 words) are chosen from the Index Medicus.
	Original Article
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	Review
	☐ The abstract must be less than 250 words.
	Letters to the Editor
	☐ No abstract is required. Body text should not exceed 1,000 words.
	Images in Critical Care
	☐ No abstract is required. The total text should not exceed 200 words.
Text	☐ The Introduction section presents the background and purpose of this study.
	☐ All tables and figures are provided in English, and all abbreviations are explained.
	☐ All tables and figures are cited in the text in order.
	☐ All tables are included in the text file, and all figures are submitted as a separate file in "TIFF" or "JPEG" formats.
	Original Article
	☐ The text is organized into Introduction, Materials and Methods, Results, Discussion, (Acknowledgments), References.
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	☐ All references are cited in the text as numbers within brackets in the same order they appear in a reference list.
	Letters to the Editor
	☐ References list entries are limited to 5.
	Images in Critical Care
	☐ References list entries are limited to 5.
Tables	☐ Each table should be consecutively typed or printed on a separate sheet of paper in the order of citation in the text. Supply a brief title at the top of the table.
	☐ The titles of tables start with "Table 1." Footnotes should be provided consecutively in order of the information, statistics, and abbreviations.
	☐ Footnoted information should be referenced using superscript small letters (ex; a, b) in alphabetical order.
Legends of Figures and Illustrations	☐ All figures and photos should be described in the text separately.
	☐ The description order must be the same as in the footnotes in tables and should be in recognizable sentences.
	☐ In microscopic pictures, staining methods and magnification ratio should be indicated.
Consent form(s)	☐ Copyright transfer form has been signed by all authors.
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Authorship Responsibility and License Agreement Form

☐ Editorial　☐ Original article　☐ Review　☐ Letter to the editor　☐ Images in critical care

Title : _____

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