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High-flow nasal cannula for respiratory failure in adult patients

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The high-flow nasal cannula (HFNC) has been recently used in several clinical settings for oxygenation in adults. In particular, the advantages of HFNC compared with low-flow oxygen systems or non-invasive ventilation include enhanced comfort, increased humidification of secretions to facilitate expectoration, washout of nasopharyngeal dead space to improve the efficiency of ventilation, provision of a small positive end-inspiratory pressure effect, and fixed and rapid delivery of an accurate fraction of inspired oxygen (FiO2) by minimizing the entrainment of room air. HFNC has been successfully used in critically ill patients with several conditions, such as hypoxemic respiratory failure, hypercapneic respiratory failure (exacerbation of chronic obstructive lung disease), post-extubation respiratory failure, pre-intubation oxygenation, and others. However, the indications are not absolute, and much of the proven benefit remains subjective and physiologic. This review discusses the practical application and clinical uses of HFNC in adults, including its unique respiratory physiologic effects, device settings, and clinical indications.

Key Words: high-flow nasal cannula; oxygen; respiratory failure

Review Article

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INTRODUCTION

Oxygen therapy is typically delivered via low-flow systems (e.g., nasal cannulae or masks) or high-flow systems (e.g., venturi masks or nonrebreathers). The high-flow nasal cannula (HFNC) is a unique mode of noninvasive respiratory support that delivers warmed, humidified oxygen with a fraction of inspired oxygen (FiO_2) of 0.21 to 1.0 and a flow rate as high as 60 L/min. HFNC is indicated for patients with respiratory failure due to various underlying conditions.

The benefits of HFNC over conventional oxygen devices (low-flow systems [nasal cannulae or masks] and high-flow systems [Venturi masks]) and noninvasive ventilation (NIV; continuous or bilevel positive airway pressure ventilation) are improved patient comfort and physiologic advantages. The latter include improved oxygenation and ventilation, better pulmonary compliance, reduced anatomical dead space, modest positive end-expiratory pressure, more efficient respiratory effort, reduced work of breathing, and improved secretion clearance [1]. The goal of this review is to examine research on HFNC in adult patients, with an emphasis on its physiological effects, titration of the device, and varied clinical applications.

PHYSIOLOGIC EFFECTS

Supplemental oxygen therapy is the first-line therapy for respiratory failure. Generally, oxygen is provided via low-flow systems (nasal cannulae or masks). However, several disadvantages have been reported relative to high-flow systems, including low efficacy and low tolerance of oxygen delivery. Bubble humidifiers are commonly used with low-flow systems for spontaneously breathing patients, but because the absolute humidity is low, patients still report discomfort, especially dry nose, dry throat, and nasal pain [2,3]. Insufficient heating and humidification also result in poor compliance with these devices. Finally, with conventional treatments in patients with respiratory failure, a disparity exists between the delivered oxygen flow and the inspiratory flow of the patient. The oxygen flow is delivered at a maximum of 15 L/min, while the inspiratory flow in these patients ranges from 30 L/min to greater than 100 L/min. As a consequence of this large disparity, the fraction of inspired oxygen (FiO_2) is variable and frequently lower than intended.

Gas from an air/oxygen blender is heated, actively humidified, and then delivered via a heated circuit. The blender can generate a flow as high as 60 L/min. The physiological effects of gas administered in this manner are outlined in Table 1.

Anatomical Dead Space Washout

HFNC can flush out the expired carbon dioxide accumulated in the anatomical dead space of the nasopharynx. This decreased accumulation can improve the efficiency of ventilation and thoracoabdominal synchrony and enhance oxygen delivery [4-6]. Thus, improved washout with HFNC relative to other oxygen delivery systems permits a larger fraction of minute ventilation to participate in alveolar gas exchange.

Table 1. Advantages and disadvantages of high-flow nasal cannula treatment

Advantage	Disadvantage
Comfort due to similarity of humidified, warmed air to physiologic conditions of the airway	Potential discomfort due to high flow and relatively hot air sensation
Carbon dioxide washout (reduced anatomical dead space)	Not immediately available
Clinician can set precise fraction of inspired oxygen.	Aerosol-generating procedure that can potentially increase the risk of viral transmission
Provides low positive end expiratory pressure effect	
Leaves mouth free for talking, eating, or coughing	

Positive End Expiratory Pressure Effect

HFNC is an open system; however, the high rate of flow from the cannula resists expiratory airflow and elevates the airway pressure [7]. In adults, as in neonates and infants, HFNC has been shown to exhibit the "positive end expiratory pressure (PEEP) effect," in which it raises the peak nasopharyngeal airway pressure present at the end of expiration [8-10], particularly when the mouth is closed. This "PEEP effect" can reduce the work of breathing, mitigate auto-PEEP (if present), and improve oxygenation. Each added increment of 10 L/min of oxygen flow adds approximately 0.7 cm H_2O (up to approximately 3 cm H_2O) of PEEP when the patient's mouth is closed and 0.35 cm H_2O when it is open [11].

Fraction of Inspired Oxygen

Physiologically, inspiratory flow and tidal volume vary breath-by-breath [12]. Patients with respiratory failure demand higher inspiratory flow rates that exceed the flow rates of standard oxygen supply devices, resulting in the entrainment of room air and a reduction in the FiO_2 of the delivered gas. The FiO_2 level varies during low-flow oxygen delivery and is generally much lower than predicted by equipment algorithms [13,14]. However, with HFNC, the gas flow rate to the patient is much higher than with low-flow oxygen systems. High flow rates minimize the entrainment of room air, yielding more accurate delivery of oxygen, especially relative to conventional delivery systems. Additionally, elevated flow rates have been demonstrated to lower the respiratory rate while increasing tidal volume, improving the overall pattern of breathing [9,15].

Humidification

HFNC ventilation systems typically include a heated humidifier. This allows these devices to deliver optimally heated and humidified gas to patients better than conventional oxygen systems. The added humidification increases the mucosal water content, aiding in the removal of secretions and potentially reducing the work of breathing. This also moistens the airway, avoiding the epithelial injury associated with airway desiccation [16,17].

Small Pliable Nasal Prongs (Comfortable Interface)

HFNC exhibits outstanding acceptance and tolerability resulting from its uniquely soft and pliable nasal prongs (Figure 1). As such, several studies have described greater patient comfort with HFNC than with conventional low-flow or high-flow oxygen administered through a face mask or nasal can-

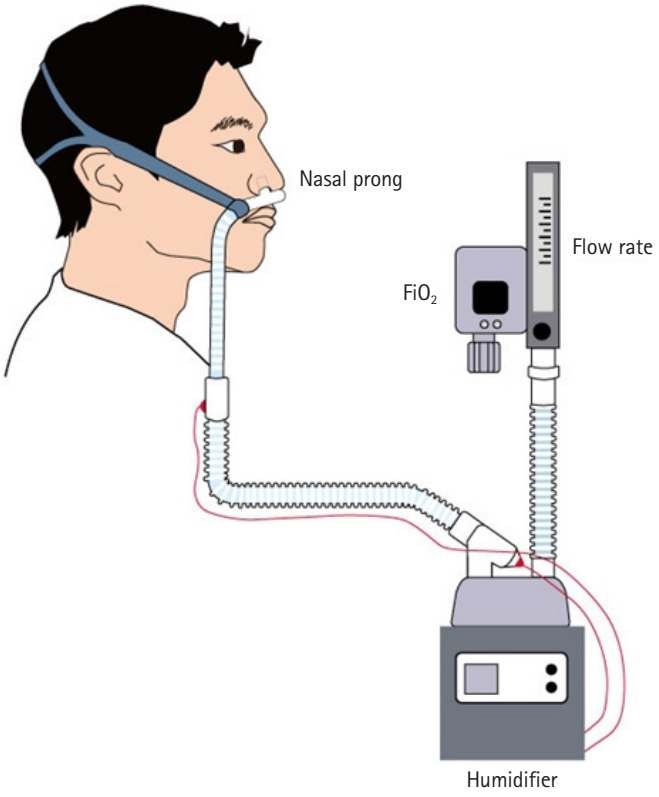

Figure 1. High-flow nasal cannula oxygen device. An air/oxygen blender, allowing a fraction of inspired oxygen (FiO_2) from 0.21 to 1.0, generates flow up to 60 L/min. The gas is heated and humidified by an active heated humidifier used during mechanical ventilation. The patient breaths medical gas through a unique large-diameter pliable nasal cannula with a single-limb heated inspiratory circuit.

nula [18-20]. NIV, in turn, is difficult to manage for extended durations, making HFNC an exciting potential alternative for do-not-intubate patients.

CLINICAL SETTINGS (DEVICE TITRATION)

HFNC is increasingly used to deliver oxygen to critically ill patients, especially those experiencing respiratory failure. However, no recommendations have been established for its practical application. Although HFNC can be administered on an unmonitored floor, it is usually applied in a monitored setting such as the intensive care unit (ICU), intermediate care wards, or emergency department [6,17].

Oxygen gas is adequately heated and humidified and is then delivered through a unique wide-bore nasal cannula, generally made of softer, more pliable plastic than the cannulae for low-flow systems. The cannula fits snugly into the snares and is held in place with a head strap (Figure 1).

Two parameters must be set: the flow rate and the FiO_2. The flow rate should be set first, typically at 20 L/min to 35 L/min (range, 5–60 L/min). Second, the FiO_2 (range, 21%–100%) is set to target a desired peripheral oxygen saturation. The flow rate can subsequently be increased in 5 to 10 L/min increments if the respiratory rate fails to improve, oxygenation fails to adequately improve, or breathing remains labored. Both increasing the flow rate and increasing the FiO_2 will result in improved peripheral oxygen saturation. We recommend maximizing the flow rate first and attempting to keep the FiO_2 ≤60%; however, an increase in FiO_2 may be necessary to achieve adequate oxygenation.

HFNC is generally well tolerated and can be administered for several days. Patients can be switched to a low-flow system (nasal cannula or mask) once the flow rate reaches 20 L/minute or lower and FiO_2 reaches 50% or lower.

CLINICAL APPLICATIONS

Acute Hypoxemic Respiratory Failure

HFNC versus low-flow oxygen

The indication of HFNC is supported by randomized trials and observational studies of patients with hypoxemic respiratory failure. While data are conflicting, these studies consistently demonstrate improved oxygenation and a decreased need for intubation when HFNC is used relative to low-flow oxygen systems [4,5,18,21-34]. However, studies have failed to show consistent and convincing benefits for mortality, length of ICU and hospital stay, dyspnea, and comfort.

The High Flow Nasal Oxygen Therapy in Resuscitation of Patients with Acute Lung Injury (FLORALI) trial was a large multicenter randomized study in which HFNC was compared with conventional oxygen therapy and NIV [22]. Adults with no prior history of lung disease and respiratory failure were randomly assigned to receive HFNC therapy, oxygen via a nonrebreather face mask, or NIV. Ultimately, the intubation rate (the primary endpoint) was similar among treatment modalities. However, other outcomes included 90-day mortality and ventilator-free days, both of which were notably lower among the patients treated with HFNC than in those treated with NIV or conventional oxygen therapy. In a post hoc examination, HFNC was also associated with lower intubation rates among patients with a partial pressure of oxygen (PaO_2)/FiO_2 ratio lower than 200. However, because overall intubation rates were lower than anticipated, the power of the study was insuf-

ficient to address this question. Finally, in examining whether delays in intubation that could influence treatment outcomes had been present, the authors concluded that the time to intubation did not differ significantly between HFNC and NIV.

Another important randomized trial involving HFNC was the Randomized Controlled Trial of Humidified High-Flow Nasal Oxygen for Acute Respiratory Distress in the Emergency Department; HOT-ER study, which described the early initiation of HFNC in 322 emergency room patients with hypoxemia. Compared with conventional oxygen therapy, the investigators found that HFNC was not superior [21]. HFNC was associated with lower intubation rates after 24 hours (HFNC, 5.5%; conventional oxygen treatment, 11.6%), although this disparity was not statistically significant (P=0.053). The groups exhibited similar 90-day mortality rates (HFNC, 21.2%; conventional oxygen treatment, 17.4%).

The conflicting results between the FLORALI and HOT-ER trials may relate to key differences in study design and patient characteristics, such as underlying comorbidities. In the FLORALI trial, the most common cause of respiratory failure was pneumonia (approximately 80% of patients). In contrast, in the HOT-ER study, only approximately one-fourth of patients had pneumonia. Additionally, over half of the HOT-ER study participants were diagnosed with asthma, heart failure, or chronic obstructive lung disease (COPD), diagnoses that were exclusion criteria for the FLORALI trial. In the FLORALI study, participants received 48 hours of continuous HFNC, while HOT-ER lacked any specific HFNC treatment protocol, potentially resulting in insufficient HFNC treatment in the latter study. HOT-ER also did not compare HFNC with NIV. In addition, the studies differed in the details of the high flow settings used; for instance, the flow rate was set 10 L/min lower in the HOT-ER than in the FLORALI protocol. Although a small disparity, the greater flow rate in the FLORALI study may have improved CO_2 clearance among the participants, reducing the work of breathing and leading to fewer intubations.

In a meta-analysis of 14 trials, the authors compared HFNC with conventional oxygen therapy in patients with acute hypoxemic respiratory failure. HFNC treatment had little or no impact on the intubation rate (26% in both groups; odds ratio, 0.98; 95% confidence interval [CI], 0.34–2.82) or the mortality rate (26% for HFNC vs. 27% for conventional oxygen therapy; relative risk [RR], 0.97; 95% CI, 0.82–1.14) [35]. The same meta-analysis also reported reduced dyspnea and improved comfort among the HFNC group as well as a possible reduction in hospital-acquired pneumonia, but the effects on ICU admissions and length of stay were uncertain.

In another meta-analysis of nine trials that compared HFNC to low-flow oxygen in patients with hypoxemic respiratory failure, HFNC was associated with a decreased need for both intubation (RR, 0.85; 95% CI, 0.74–0.99) and escalation of respiratory support (RR, 0.71; 95% CI, 0.51–0.98) [36]. However, no differences were observed in the mortality rate, length of stay, or patient dyspnea and comfort.

Moreover, in a network meta-analysis, HFNC was shown to reduce the intubation rate in patients with acute hypoxemic respiratory failure compared with conventional low-flow oxygen, but no impact was observed on mortality (RR, 0.76; 95% CI, 0.55–0.99) [37].

HFNC versus NIV

Conflicting evidence exists about whether NIV is beneficial to patients with hypoxemic nonhypercapnic respiratory failure [38-46]. A network meta-analysis of 25 randomized trials examined outcomes in patients with acute hypoxemic respiratory failure who were treated with noninvasive modalities (helmet NIV, facemask NIV, and HFNC) compared with those of patients who were treated with low-flow oxygen [37]. Mortality was lower among patients treated with helmet or face mask NIV than in those treated with low-flow oxygen (helmet NIV: RR, 0.40; 95% CI, 0.24–0.6; face mask NIV: RR, 0.83; 95% CI, 0.68–0.99). All three noninvasive modalities were associated with lower intubation rates (helmet NIV: RR, 0.26; 95% CI, 0.14–0.46; face mask NIV: RR, 0.76; 95% CI, 0.62–0.90; HFNC: RR, 0.76; 95% CI, 0.55–0.99). However, this network meta-analysis should be interpreted with caution due to significant heterogeneity and risk of bias due to lack of blinding, as well as a wide range of etiologies for respiratory failure and illness severity among participants. In addition, the mortality benefit was not found among patients with severe hypoxemia (a PaO_2/FiO_2 ratio <200 mm Hg).

In a meta-analysis that included 29 randomized trials with mixed populations of participants who had acute respiratory failure, HFNC was compared with NIV [42]. HFNC was associated with lower rates of mortality (RR, 0.44; 95% CI, 0.24–0.79), intubation (RR, 0.71; 95% CI, 0.53–0.95), and possibly hospital-acquired pneumonia (RR, 0.46; 95% CI, 0.15–1.45) and improved patient comfort. However, interpretation of the analysis is limited by the small sample size and heterogeneity in the study design, patient population characteristics, type of respiratory failure, and outcomes. Despite these limitations, HFNC appears to be at least non-inferior and is an acceptable choice

in this clinical setting.

With regard to devices, helmet NIV was compared with HFNC in another small study of severely hypoxemic patients [34]. Helmet NIV was associated with greater improvements in oxygenation, a reduction in dyspnea and respiratory effort, and similar levels of $PaCO_2$.

Concerns have been raised regarding whether the use of HFNC can potentially delay necessary intubation and worsen outcomes [47]. As a result, when HFNC is used, clinicians should remain vigilant to signs of respiratory failure that necessitate intubation and mechanical ventilation. Patients who are not tachypneic may experience success with HFNC despite a relatively high FiO_2. The ROX index (peripheral arterial oxygen saturation/fraction of inspired oxygen [expressed as a percentage]/respiratory rate) may also help guide clinicians in this regard. In one small series, a ROX index of >4.88 at 2, 6, and 12 hours after initiation of HFNC was shown to indicate a lower likelihood of subsequent endotracheal intubation. Further studies are needed to validate the value of ROX in this population before it can be routinely used.

Acute Hypercapnic Respiratory Failure

Hypercapnic respiratory failure is another frequent clinical situation that can arise from acute exacerbation of COPD. For patients with this condition, when other oxygen devices have failed, NIV has been the primary treatment for respiratory support before endotracheal intubation. However, because of poor mask compliance, it is inappropriate for some patients [48,49]. Among these patients with hypercapnic respiratory failure, since HFNC tends to be well-tolerated, it can frequently be utilized to manage the condition successfully [50].

Although HFNC does not provide active inspiratory support in COPD patients, the technique has been shown to increase tidal volume [51]. Nilius et al. [52] found varied effects of HFNC on hypercapnic respiratory failure from COPD; for some individuals, the frequency of breathing was depressed, while for others, $PaCO_2$ was lowered. Among stable patients with COPD, HFNC also increases the capacity for exercise, providing improved oxygenation relative to spontaneous breathing [53]. These results suggest that, for certain forms of hypercapnic respiratory failure, HFNC is an extremely promising therapeutic option.

Pre-intubation Oxygenation

During intubation support, preoxygenation is routinely used to prevent desaturation. Most experts use conventional systems and bag-mask ventilation to deliver oxygen prior to intubation; the bag mask or oxygen mask is temporarily removed for the intubation procedure. Although not routine, HFNC is an acceptable method to provide oxygen to patients undergoing intubation, both before (preoxygenation) and during the procedure (to prevent desaturation). However, data regarding the value of HFNC for preoxygenation prior to intubation are conflicting [54-57].

Several trials have shown improved oxygenation when HFNC strategies are used. One randomized single-center study compared 4 minutes of preoxygenation with HFNC (100% FiO_2 at 60 L/minute) together with concomitant NIV (10 cm H_2O pressure support ventilation and 5 cm H_2O PEEP) with NIV alone prior to intubation. HFNC/NIV was associated with higher peripheral oxygen saturation (100% vs. 96%) and fewer patients with episodes of desaturation below 80% (0% vs. 21%) [54]. Miguel-Montanes et al. [55] reported similar results in a study of 101 patients, where compared with a nonrebreather mask, peripheral oxygen saturation levels at the end of the preoxygenation period were higher with HFNC (100% vs. 94%) and fewer patients exhibited episodes of severe hypoxemia (2% vs. 14%). Overall, HFNC was associated with a significant decrease in the prevalence of severe hypoxemia, and the authors concluded that its application could improve the safety of patients while they are intubated in the ICU.

In contrast, in a multicenter study of 124 patients undergoing intubation who had severe hypoxemia (PaO_2/FiO_2 ratio <300 mm Hg, respiratory rate >30 breaths/min, and a FiO_2 >50% to achieve a saturation of >90%), HFNC did not reduce the lowest saturation during intubation when compared with preoxygenation using a conventional high-flow oxygen face mask [56]. The discordant results may be explained by differences between the studies in the indications for intubation and severity of hypoxemia prior to intubation.

Post-extubation (Preventing Re-intubation)

Every patient should be oxygenated following extubation. For most patients, this goal is achieved with low-flow systems (nasal prongs or simple masks). When a higher-flow system is required, Venturi masks or HFNC may be applied. The choice of oxygen devices should be individualized and depends on factors including oxygen requirement, the etiology of respiratory failure, and patient preferences.

The efficacy of HFNC in the post-extubation periods was best illustrated in a trial of 527 patients (mixed postsurgical and medical) at low risk for reintubation following extubation.

For 24 hours post-extubation, HFNC was associated with less frequent reintubations than occurred when conventional oxygen was used (4.9% vs. 12.2%), as well as improved secretion clearance, with 14 patients needed to treat to prevent 1 reintubation [57]. In patients at high risk for reintubation, HFNC and NIV were compared in a randomized trial of 604 patients (mixed surgical and medical populations). After 72 hours, 22.8% of the HFNC group required reintubation compared to 19.1% in the NIV group [58]. While the length of the ICU stay was lower in those treated with HFNC, no differences were observed in the rates of mortality, sepsis, or multiorgan failure. Additionally, although 20% of participants in this trial were patients with moderate to severe COPD, these data are insufficient to make a robust recommendation in favor of HFNC for patients with COPD with chronic hypercapnia, a population in which the evidence and guidelines favor NIV.

A meta-analysis of 9 trials reported that HFNC was associated with reduced reintubation rates (RR, 0.46; 95% CI, 0.30–0.70) and incidence of post-extubation respiratory failure (RR, 0.52; 95% CI, 0.30–0.91) compared with conventional oxygen therapy [59]. However, compared with NIV, HFNC is not superior to NIV with regard to the rates of reintubation or post-extubation respiratory failure.

Postoperative Respiratory Failure

Postoperative respiratory failure accounts for more than 20% of all patients receiving ventilatory support [60,61]. Respiratory failure requiring unplanned reintubation in the postoperative period is associated with high morbidity, leading to a longer hospital stay and an increase in 30-day mortality [62-64]. The risk of reintubation was greatest within the first 6 hours after primary extubation, with consequences such as pneumonia (including aspiration), pulmonary edema, atelectasis, airway obstruction, and impaired brain function.

Generally, moderate evidence favors NIV as a technique for the prevention of reintubation in this situation [65]. Consequently, randomized trials evaluating the efficacy of HFNC are lacking; thus, HFNC is not typically used as a first-line therapy to prevent or manage postoperative respiratory failure. That said, it may be a reasonable alternative, particularly for patients who do not tolerate NIV well.

Hernández et al. [57] reported that the immediate application of HFNC was associated with a lower risk of respiratory failure and reintubation at 72 hours when compared with conventional oxygen therapy. In a study by Corley et al. [66], 155 obese patients (body mass index 30 kg/m^2) undergoing cardiopulmonary bypass surgery were assigned to either the HFNC group (35–50 L/min) or the nasal cannula or face mask group (2–6 L/min) for 8 hours post-extubation. The groups were similar with regard to oxygenation, dyspnea, and the radiographic features of atelectasis. In another study, Yu et al. [67] compared HFNC with conventional oxygen treatment after thoracoscopic lobectomy. A total of 110 patients at moderate to high risk of reintubation were randomized postoperatively to receive either HFNC (35–60 L/min) or low-flow oxygen administered via nasal cannula or face mask. HFNC treatment was associated with a lower rate of hypoxemia (12% vs. 29%) and a decreased need for NIV (4% vs. 17%). Among the participants receiving conventional oxygen therapy, five reintubations were required, compared with none in the HFNC group.

In a study comparing HFNC with NIV, 830 patients who either developed or were at risk of developing acute respiratory failure after cardiothoracic surgery were randomly assigned to receive either HFNC or NIV. The HFNC treatment was conducted at 50 L/min and an FiO_2 of 50%, whereas NIV involved bilevel positive airway pressure for at least 4 hours each day (pressure support, 8 cm H_2O; PEEP, 4 cm H_2O) [68]. No statistically significant differences were observed between the HFNC and NIV groups in treatment failure rate (reintubation, switch to the other treatment, or treatment discontinuation; HFNC 21% and NIV 22%). Similarly, the mortality rates were not statistically different (7% and 6%, respectively). However, skin breakdown, as expected, was more commonly encountered with NIV (10% vs. 3%).

In a meta-analysis of seven randomized trials involving 2,781 patients, HFNC was associated with a similar reintubation rate to both conventional oxygen therapy (RR, 0.58; 95% CI, 0.21–1.60) and NIV (RR, 1.11; 95% CI, 0.88–1.40) [69]. However, in a subgroup analysis of critically-ill patients, the HFNC group exhibited a lower reintubation rate than the conventional oxygen therapy group (RR, 0.35; 95% CI, 0.19–0.64).

In another meta-analysis of 14 studies, HFNC was associated with a statistically insignificant reduction in intubation rate and a reduction in length of hospital stay [70]. In contrast, in a subsequent meta-analysis of 9 trials, compared with conventional oxygen therapy, the use of HFNC postoperatively lowered reintubation rates (RR, 0.32; 95% CI, 0.12–0.88) and decreased the need to escalate respiratory support (e.g., switching to NIV; RR, 0.54; 95% CI, 0.31–0.94) [59]. However, HFNC had no effect on mortality rate, length of ICU or hospital stay, or rate of postoperative hypoxia.

Acute Hypoxemic Respiratory Failure in Immunosuppressed Patients

The mortality rate is relatively high among immunosuppressed patients with acute respiratory failure who need mechanical ventilation [71]. In this situation, NIV is recommended as first-line therapy, and it has been found to be effective in relieving sensations of dyspnea. In two studies, results have indicated that NIV is associated with less frequent intubations and lower mortality relative to conventional oxygen therapy [72].

A post hoc examination of the FLORALI study [27] indicated that among immunosuppressed patients, NIV was associated with more frequent intubation and a higher mortality rate than conventional oxygen therapy or HFNC [23]. A retrospective study of patients with cancer suggested that HFNC treatment was associated with a lower 28-day mortality rate than treatment with conventional oxygen therapy, NIV, or both (35% in the HFNC group vs. 57% in the non-HFNC group) [73]. When HFNC was compared with NIV as first-line therapy in a prospective observational study, it was found to be associated with reduced frequency of intubation (35% vs. 55%, respectively) and reduced mortality (20% vs. 40%, respectively) [74]. Notably, however, HFNC was not effective as a rescue treatment after the failure of conventional oxygen therapy or NIV [24], indicating that HFNC is best suited for early application.

Additionally, HFNC has been observed to reduce the rate of respiration and dyspnea in immunosuppressed patients, resembling its effects in patients who are not immunosuppressed [26,75-77]. Thus, HFNC may be a more easily tolerated alternative device that can provide adequate oxygenation and effective palliation, even for those immunosuppressed, "do not intubate" patients.

Acute Hypoxemic Respiratory Failure in COVID-19

When the oxygen requirement or work of breathing is increased, treatment options are HFNC, an NIV device, or invasive mechanical ventilation after intubation. Generally, clinical physicians favor noninvasive modalities (HFNC or NIV) over invasive mechanical ventilation.

While one retrospective study reported reduced rates of intubation and mechanical ventilation with HFNC [78], another retrospective study including noninvasive modalities reported no differences in the intubation rate for patients for coronavirus disease 2019 (COVID-19) treated with HFNC (29%), continuous positive airway pressure (25%), or other modes of NIV (28%) [79]. Additionally, no differences in mortality were observed.

Grieco et al. [80] compared helmet NIV and HFNC in 110 individuals with moderate to severe acute hypoxemic respiratory failure due to COVID-19. No significant difference was observed in days free of respiratory support at the 28-day mark (helmet NIV, 20 days; HFNC, 18 days). However, patients receiving helmet NIV had lower rates of intubation (30% vs. 51%) and experienced more days free of invasive mechanical ventilation (28 vs. 25 days).

HFNC is an aerosol-generating procedure that can potentially increase the risk of viral transmission. In spontaneously breathing patients with suspected or documented COVID-19, when HFNC is used, airborne in addition to standard precautions should be undertaken (i.e., full personal protective equipment; placing a surgical mask on the patient during HFNC when health care workers are in the room or the patient is being transported, or starting at the lowest effective flow rate).

CONTRAINDICATIONS

No randomized clinical trials have reported contraindications of HFNC as a primary endpoint. As such, no absolute contraindications have been identified. Relative contraindications to HFNC include any factor that prevents a nasal cannula from being appropriately fitted, such as irregularities of the nose, face, or airway or a history of surgery of those regions. Some experts avoid HFNC following upper airway surgery to avoid the theoretical risk that the high pressure may precipitate venous thromboembolism.

CONCLUSIONS

The HFNC is a method of respiratory support in which a high flow of humidified and heated oxygen is delivered at a set concentration via a unique device. HFNC is being increasingly used for patients with respiratory failure of diverse etiologies.

The advantages of HFNC over conventional oxygen systems or NIV include improved comfort, the facilitation of expectoration due to greater humidification of secretions, the washout of upper respiratory dead space to improve ventilation efficiency, a small positive airway pressure effect, and high flow rates to minimize the entrainment of room air for reliable delivery of FiO_2.

HFNC has been successfully used in several settings such as severe acute respiratory failure, extubation failure, peri-intubation, postoperative respiratory failure, and others. However,

the indications are not absolute, with much of the proven benefit subjective and physiologic. The choice of oxygen delivery system should be patient-specific, and factors to consider include institutional availability, clinicians' judgment, patients' preferences, the level of necessity for ventilation and PEEP, and hypoxemic severity.

CONFLICT OF INTEREST

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

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Critical care management of pulmonary arterial hypertension in pregnancy: the pre-, peri- and post-partum stages

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The mortality rate of pulmonary hypertension in pregnancy is 25%–56%. Pulmonary arterial hypertension is the highest incidence among this group, especially in young women. Despite clear recommendation of pregnancy avoidance, certain groups of patients are initially diagnosed during the gestational age step into the third trimester. While the presence of right ventricular failure in early gestation is usually trivial, it can be more severe in the late trimester. Current evidence shows no consensus in the management and serious precautions for each stage of the pre-, peri- and post-partum periods of this specific group. Pulmonary hypertension-targeted drugs, mode of delivery, type of anesthesia, and some avoidances should be planned among a multidisciplinary team to enhance maternal and fetal survival opportunities. Sudden circulatory collapse from cardiac decompensation during the peri- and post-partum phases is detrimental, and mechanical support such as extracorporeal membrane oxygenation should be considered for mitigating hemodynamics and extending cardiac recovery time. Our review aims to explain the pathophysiology of pulmonary arterial hypertension and summarize the current evidence for critical management and precautions in each stage of pregnancy.

Key Words: extracorporeal membrane oxygenation; heart decompensation; pregnancy; pulmonary arterial hypertension; right-sided heart failure; vasodilator agents

Review Article

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INTRODUCTION

Pulmonary arterial hypertension (PAH) often leads to acute right ventricular failure, circulatory collapse and death during in pregnancy [1,2]. The incidence of PAH in pregnancy has ranged from less than 1% to 8%, and maternal mortality (9%–33%) is highest among pregnancies coexisting with cardiac disease [3-6]. The manifestations of undiagnosed PAH during pregnancy are difficult to distinguish from the normal physiologic changes of pregnancy, such as palpitations, exertional dyspnea and lower extremity edema [7]. When the symptoms of right ventricular failure are detected late in these patients, the appropriate treatment is delayed [8,9]. The hemodynamic changes during the peri- and post-partum pe-

riods cause the majority of maternal morbidity and mortality as a result of increased cardiac output [10]. In this particular context, cardiac decompensation consists of acute right ventricular failure, cardiogenic shock, and cardiac collapse. Referral to a pulmonary hypertension center that uses a multidisciplinary team approach (obstetrician, cardiologist, pulmonologist, anesthesiologist, cardio-thoracic surgeon, intensivist, and pediatrician) should be considered as necessary to improve outcomes.

PATHOPHYSIOLOGY OF CARDIAC DECOMPENSATION IN PREGNANT PATIENTS WITH PAH

Pre-partum Stage

In 2nd to 3rd trimester of gestation, a normal physiologic change contributes to surging cardiac output as a result of increased stroke volume, heart rate and total blood volume. The maternal blood volume rises approximately 45% (1,200 to 1,600 ml) with the highest in the 3rd trimester (32–34 weeks) [7,11]. The gestational hormones estrogen and progesterone are produced by the placenta and have a vasodilator effect through membranous ion channels, relating to decreased systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) [12-14]. Recorded by transthoracic echocardiography (TTE), PVR reduction is mostly in the third trimester by 17.5% [7]. The effect of low SVR and PVR during pregnancy mitigates cardiac decompensation in PAH patients from high cardiac output. However, the effect of vasodilation incompletely ameliorates the detrimental result from right ventricular failure when patients enter the last trimester. The late 2nd to 3rd trimester and postpartum are the two critical phases of cardiac decompensation in pregnant patients with PAH [15]. In addition, physiologic anemia during pregnancy and hormonal effect decrease myocardial oxygen supply, contributing to right ventricular wall stress and remodeling (Figure 1) [16].

Peri-partum Stage

During labor, the cardiac output and systemic blood pressure rise with each uterine contraction [17], and auto-transfusion returns of 300–500 ml of blood into the systemic circulation. The sympathetic response to pain and anxiety also elevates maternal blood pressure and heart rate [11]. The overwhelming venous return and rising systemic resistance directly affect right ventricular function. The prolong secondary stage of labor and the Valsalva maneuver are known as negative risk

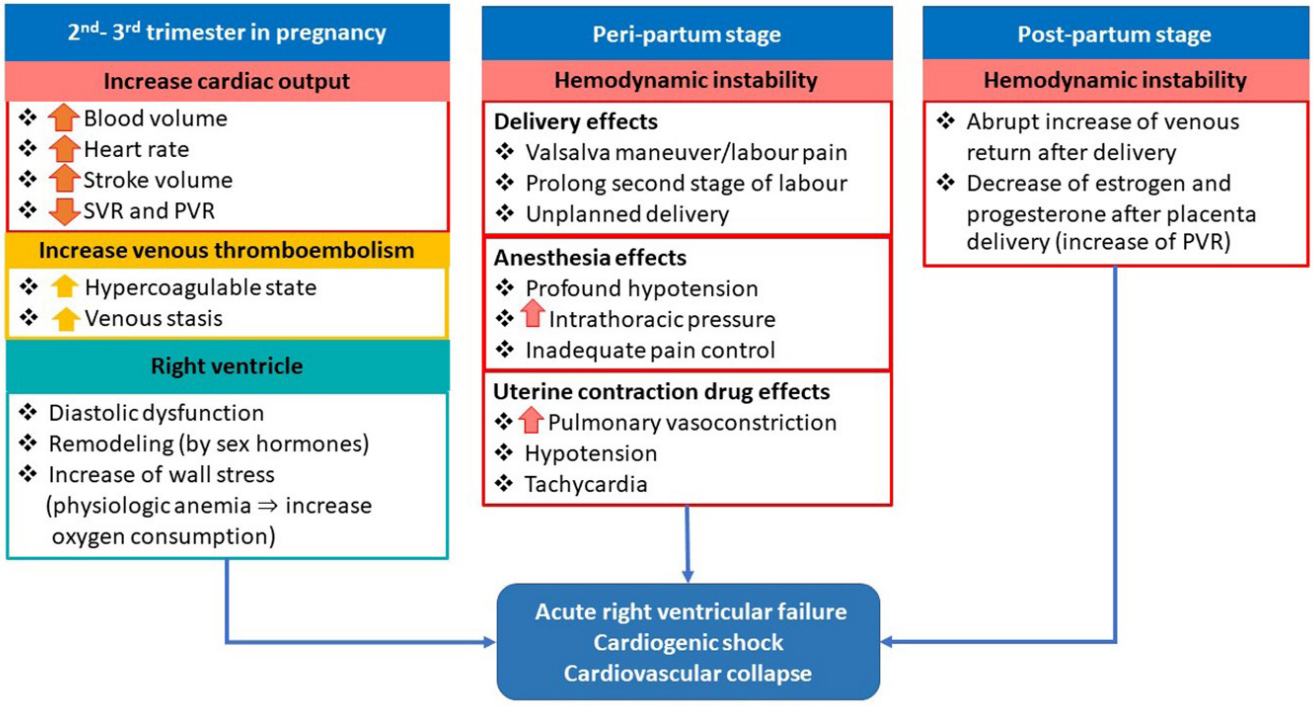

Figure 1. Pathophysiology of acute right ventricular failure, cardiogenic shock, and cardiovascular collapse in pregnant patients with pulmonary arterial hypertension (PAH) during the pre-, peri- and post-partum stages. SVR: systemic vascular resistance; PVR: pulmonary vascular resistance.

factors [18] as well as anesthetic methods due to the increased intrathoracic pressure and PVR. These effects predispose to acute right ventricular failure and profound hypotension.

Post-partum Stage

After delivery, an abrupt increase of venous return (500 ml) from inferior vena cava decompression returns to the heart, resulting in decompensation of an unhealthy right ventricle [11,15]. In addition, a fall of estrogen and progesterone levels after placenta delivery directly affects the pulmonary venous resistance. An abrupt rise of pulmonary venous resistance obscures fluid flow from right-to-left circulation, leading to cardiac decompensation.

CRITICAL CARE MANAGEMENT OF CARDIAC DECOMPENSATION IN PREGNANT PATIENTS WITH PAH

Pre-partum Stage

PAH-targeted therapy

A pulmonary vasodilator, which reduces right ventricular afterload and improves cardiac function, is an important treatment of PAH [19]. There are three main mechanisms of PAH treatment: cyclic adenosine monophosphate, cyclic guanosine monophosphate and endothelin pathway [20]. However, the endothelin receptor antagonist group is a contraindication in pregnancy due to its teratogenic effects (category X). The following drugs are commonly administered in pregnancy. (1) Cyclic adenosine monophosphate pathway: (a) inhaled nitric oxide (iNO), (b) phosphodiesterase 5 inhibitor; sildenafil (category B) is commonly used in combination with prostaglandin, (c) guanylate cyclase stimulator is category X. (2) Cyclic guanosine monophosphate pathway: (a) prostacyclin derivatives; intravenous epoprostenol, inhaled iloprost.

The severity of patients who haven't received treatment is classified by the World Health Organization functional classification (WHO FC) I to IV. Patients with WHO FC I–II should be treated with oral sildenafil and closely monitored, while WHO FC III-IV patients require hospital admission and administration of either intravenous prostacyclin derivatives or combined therapy (Table 1).

Close monitoring

In the pre-delivery stage, TTE should be used for daily monitoring to detect early cardiac decompensation and evaluate fluid status. An arterial line and a central venous catheter can also be considered for hemodynamic monitoring, while a pulmonary artery catheter is not routinely required.

Anticoagulant

Due to their hypercoagulable state, these patients have a high risk of venous thromboembolism as acute pulmonary embolism and deep vein thrombosis during both pregnancy and the post-postpartum period [21]. As a result of increased estrogen levels, blood coagulation Factors 7, 8, 9, 10, 12, 13 and von Willebrand factor are markedly elevated, which significantly increases in the third trimester [11]. Additionally, the increased levels of several plasminogen inhibitors diminish the overall fibrinolytic capacity [22,23]. While blood coagulation inhibitors are unpredictable, their effects during pregnancy result in unchanged antithrombin and protein C levels and a markedly decreased protein S level. The reduction of venous flow in the lower limbs is another precipitating risk [11]. Consequently, it is recommended that PAH patients

Table 1. WHO FC-related PAH-targeted drugs in pregnancy

Severity WHO FC	Type of medication	Route	Dosage	Pregnancy category
FC I–II	Phosphodiesterase 5 inhibitor: sildenafil	Oral	20–150 mg/day [24]	B
FC III	Prostacyclin derivative: iloprost	Inhaled (ultrasonic nebulizer)	3–20 μg/day (7–9 times/day) [25]	C
FC IV	Prostacyclin derivative: epoprostenol	Intravenous	Initiate at 2 ng/kg/min and gradually increase up to 20 ng/kg/min [26] (maximally tolerated dosage based on clinical symptoms and adverse effects)	B
	May combine with sildenafil [27]			
	Nitric oxide	Inhaled	5–20 PPM [28]	C
	May combine with sildenafil [29]			

WHO: World Health Organization; FC: functional classification; PAH: pulmonary arterial hypertension.

with pregnancy in the antepartum through postpartum periods should be treated with low molecular weight heparin [2,9,30,31]. Unfractionated heparin should also be considered, especially in the unpredictable peri-partum phase.

Peri-partum Stage

Mode of delivery: vaginal delivery vs. caesarean section

The gestation of 32 to 36 weeks is preferable for delivery [1,9] because of its many advantages, such as accessibly promoting fetal lung growth, absence of uterine contraction and well-planned delivery. Cardiac stabilization with an adequate PAH-targeted therapy and resuscitation are necessary to reduce maternal and fetal mortality. The mode of delivery between vaginal delivery (the previous decade) and caesarean section (the present) remains controversial [31,32]. Although the benefits of vaginal delivery consist of smaller blood volume loss, lower bleeding complication, lower infection rate, and less altered hemodynamics than caesarean section [9,33,34], it has some serious complications. First, labor pain could overstimulate the sympathetic nervous system. Second, the Valsalva effect during delivery could worsen maternal cardiac function due to low cardiac output by increasing intrathoracic pressure and thus decreasing venous return [35]. Currently, elective caesarean section is considered as a mode of delivery due to better control of hemodynamic outcomes and delivery duration [3,36,37].

Anesthetic management: regional anesthesia vs. general anesthesia

There are many adverse effects from general anesthesia, especially increases of pulmonary arterial pressure and PVR during laryngoscopy and tracheal intubation. In addition, the positive pressure ventilation on venous return may lead to hemodynamic instability [3,38]. Regional anesthesia is commonly used by combining the spinal and epidural approach to provide ultimately effective anesthesia to minimize the dose of anesthetics [39]. Epidural anesthesia has a slow onset (15–20 minutes) but provides hemodynamic stability. In contrast, spinal anesthesia is rapid onset (1–2 minutes) but is associated with peripheral vasodilation. However, single-shot spinal anesthesia should be avoided because of its profoundly hemodynamic effect by sympathetic block [31]. Furthermore, the ultimate goal of anesthetic management is the control of pain, where hypoxemia and hypercapnia could be considered as hemodynamically sustaining effects [19,40].

Uterine contraction agents

The uterine contraction agent is a potential risk for deteriorating the circulatory system, although it can be necessary for the prevention of uterine atony [32]. In PAH patients, oxytocin should be given by infusion without a bolus dose to reduce systemic vasodilation. A slow infusion rate of oxytocin effectively minimizes the potential for hypotension, tachycardia, and fluid retention [41]. Ergotamine and prostaglandin F2 alpha should be cautiously used in PAH patients because of their effects to increase vasoconstriction, myocardial infarction and pulmonary venous congestion [15].

Post-partum Stage

Close monitoring in the intensive care unit

The majority of deaths in pregnant patients with PAH in the last decade have occurred in the post-partum period, mainly in the first to third month [31,42,43]. Most observational studies illustrated unprecedented events, such as severe right ventricular failure, hypotension, and circulatory collapse, which occurred within the first 7 days after delivery [1]. The treatment goals during the post-partum period, especially in the first 48 hours, are to avoid volume overload, maintain systemic blood pressure and closely observe right atrial pressure and cardiac function.

Medical management during cardiac decompensation

Drugs used to treat right heart failure are mostly in the Food and Drug Administration (FDA) pregnancy category C except dobutamine (category B). Fortunately, most pregnant patients with PAH develop cardiac decompensation after delivery because of the pathophysiology of increased venous return and PVR. Therefore, the treatment of right heart failure and cardiogenic shock is not significantly different from the non-pregnant group. However, the treatment of unhealthy right ventricular function and PAH largely deals with the preload sensitive character (i.e., avoiding over-corrected fluid or over diuresis), reduction in PVR as previously mentioned (optimizing afterload), and contractility promotion. The role of diuresis (furosemide is FDA pregnancy category C) may be essential in patients who have obvious pulmonary edema, and close monitoring is required. The increase of right ventricular contractility with inotropic agents has been proposed in various studies; however, there are some commonly used treatments in right heart failure that have smaller effects on the increased PVR, such as milrinone, dobutamine, and levosimendan [44-46]. In a hypotensive patient, either epinephrine or norepinephrine is

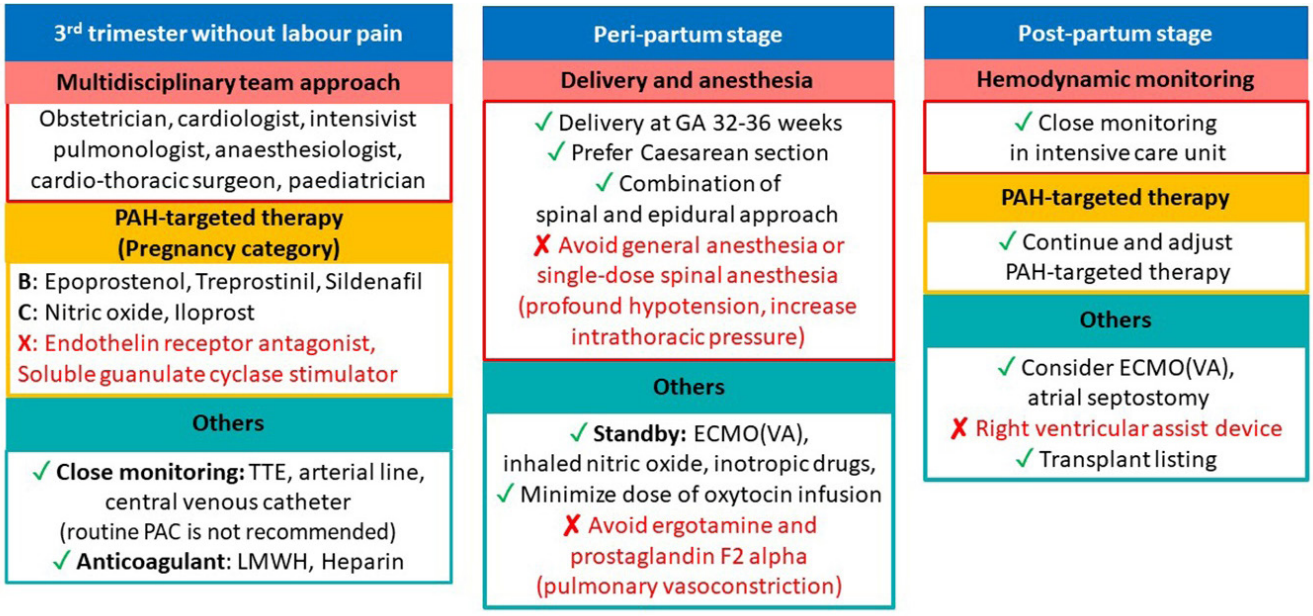

Figure 2. Critical care management for acute right ventricular failure, cardiogenic shock and cardiovascular collapse in pregnant patients with pulmonary arterial hypertension (PAH) during the pre-, peri- and post-partum stages. TTE: transthoracic echocardiography; LMWH: low molecular weight heparin; ECMO: extracorporeal membrane oxygenation; VA: veno-arterial.

preferable to add-on with minimally increased PVR concerns [47,48].

Rescue management

In a PAH patient who is unresponsive to maximal medical therapy, extracorporeal membrane oxygenation (ECMO) is a novel mechanical support for bridging to recovery or transplantation by unloading the right ventricle and enhancing oxygenation and ventilation [18,49]. While right ventricular assist device mainly supports right ventricular load without improving oxygenation and ventilation, it carries a potential to rupture the pulmonary artery. There is no current guideline on the use of ECMO during or after pregnancy [50]. The initial ECMO configurations reported in pregnancy are veno-venous, veno-arterial (VA) and veno-arterial-venous mode. However, VA-ECMO is widely considered to support hemodynamics in decompensated pregnant PAH patients, and some are extubated while continuing VA-ECMO. Although ECMO is one of the supporting procedures for recovery, time mostly being activated that was in postpartum period when refractory circulatory failure usually occurred. Several reports showed some benefits of ECMO during the peripartum stage [24,25,27,37,43,51]. Cannula size and route are also challenging for cannulation due to the anatomical changes during pregnancy. Femoral cannulation should be performed with caution, but there have been no reports of flow insufficiency from gravid uterus compression [26,43]. The duration of ECMO has been reported from 6 to 30 days, and bleeding is the most common complication [29,43]. Alternatively, atrial septostomy may be an additional method for unloading right ventricular pressure and particularly early promoting ECMO decannulation [29].

Contraception

Pregnancy is classified by the WHO in category 4 as an extremely high risk of maternal morbidity and mortality, which is an absolute contraindication of pulmonary hypertension patient [28]. Termination should be discussed if it is plausible. The current practice is focusing on outpatient counselling for pregnancy prevention, as there are many issues surrounding methods of contraception [52]. Currently, estrogen-containing contraceptives and injectable progestins are not recommended because of their potentially increased risk of venous thromboembolism, while the progestin-only pill often has a high failure rate of contraception [35,53]. Alternatively, non-permanent devices, such as progestin-only intrauterine device and implantation, are acceptable, but they have imprecise efficacy and could alter levels of pulmonary vasodilator drugs. Consequently, permanent contraception is preferable. A report from the Mayo Clinic of a retrospective cohort showed that micro-insert hysteroscopic sterilization provided an effective

advantage in patients who could undergo the procedure in an elective setting due to its small procedural risk [54]. Laparoscopic tubal ligation still requires general anesthesia [35]. Tubal ligation, however, could be performed in patients who underwent caesarean section (Figure 2).

CONCLUSION

The presence of PAH with pregnancy in the 3rd trimester leads to unavoidable morbidity or mortality. Acute right ventricular decompensation usually demonstrates either near the end of gestation or in the post-partum period. The critical care management should consist of pulmonary hypertension-targeted treatment, mode of delivery, anesthesia, and postoperative care after delivery, including promoting cardiac function with medications, rescuing therapies, and a multidisciplinary team approach to promote good maternal and fetal outcomes. Effective permanent contraception is essentially required in patients with PAH who are of childbearing age for the prevention of devastating events.

CONFLICT OF INTEREST

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

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Effect of modified care bundle for prevention of ventilator-associated pneumonia in critically-ill neurosurgical patients

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Background: Care bundles for ventilator-associated pneumonia (VAP) have been shown to minimize the rate of VAP in critically ill patients. Standard care bundles may need to be modified in resource-constrained situations. The goal of this study was to see if our modified VAP-care bundles lowered the risk of VAP in neurosurgical patients.

Methods: A prospective cohort study was conducted in mechanically ventilated neurosurgical patients. The VAP bundle was adjusted in the cohort group by increasing the frequency of intermittent endotracheal tube cuff pressure monitoring to six times a day while reducing oral care with 0.12% chlorhexidine to three times a day. The rate of VAP was compared to the historical control group.

Results: A total of 146 and 145 patients were enrolled in control and cohort groups, respectively. The mean age of patients was 52±16 years in both groups (P=0.803). The admission Glasgow coma scores were 7.79±2.67 and 7.80±2.77 in control and cohort group, respectively (P=0.969). VAP was found in nine patients in control group but only one patient in cohort group. The occurrence rate of VAP was significantly reduced in cohort group compared to control group (0.88/1,000 vs. 6.84/1,000 ventilator days, P=0.036).

Conclusions: The modified VAP bundle is effective in lowering the VAP rate in critically ill neurosurgical patients. It requires low budget and manpower and can be employed in resource-constrained settings.

Key Words: chlorhexidine; critical care; intubation; neurosurgery; oral hygiene; ventilator-associated pneumonia

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INTRODUCTION

Intubated and mechanically ventilated critically ill patients are at a high risk of acquiring ventilator-associated pneumonia (VAP), for those who have been intubated for more than 24 hours have a 6- to 21-fold increased risk of VAP [1]. The overall rate of VAP is 10 to 15 per 1,000 ventilator days and the rate is increasing at a rate of 1 to 3% every ventilator [2].

A VAP bundle has been shown to reduce the VAP rate and has become the gold standard

of care around the world [3]. Our hospital has also been using a VAP bundle called the Suandok model [4] since 2016, and it consists of six elements of care: (1) head of bed elevation by at least 30°, (2) practicing good hand hygiene, (3) checking residual gastric content before feeding, (4) implementing a ventilator weaning protocol, (5) intermittent monitoring the endotracheal tube (ET) cuff pressure three times a day, and (6) oral care with 0.12% chlorhexidine four times a day. According to our previous study, using the VAP bundle was proven to be effective in lowering the VAP rate to 13.30 per 1,000 ventilator days [4].

Recently, many institutions have implemented the use of continuous cuff pressure monitoring, and it has also been shown to be superior to intermittent cuff pressure monitoring [5,6]. This technique, however, necessitates the use of expensive monitoring equipment, which is not currently available at our institution. Furthermore, we also realized that providing oral care four times a day has a drawback in that it is time-consuming and requires manpower. For these reasons, in a setting with limited resources as in our institution, we have to modify the VAP bundle by increasing the time of ET cuff pressure monitoring to four times a day, while reducing the oral care to three times a day. In this study, we investigated whether our modified VAP bundle is as effective as or better than the previous VAP bundle.

KEY MESSAGES

- Ventilator-associated pneumonia (VAP) care bundles should be implemented in all critically ill neurosurgical patients.
- Our modified VAP care bundle has efficacy in reduction of VAP rate and can be used in settings of limited resources.

MATERIALS AND METHODS

This study was approved by the Institutional Research Ethics Committee of Faculty of Medicine, Chiang Mai University (No. SUR-2561-05638, Research ID: NUR-2561-05909, Research ID: 05909).

Setting and Study Design

A prospective cohort study was done in an eight-bed neurosurgical critical care unit and a nine-bed intermediate care neurosurgical unit.

Inclusion and Exclusion Criteria

Between November 2018 and June 2020, we enrolled all adult (over 18 years old) neurosurgical patients who met the criteria, which included being intubated and receiving mechanical ventilation for at least 24 hours, having no prior signs and symptoms of pneumonia, no contraindication for head of bed elevation, or a fractured cervical spine, and not being an end-of-life care patient. The modified VAP bundle of care was given to this cohort. Patients in the control group were those who had been treated in the same critical care unit and met the same criteria between January 2016 and the time when the modified VAP bundle was implemented. Age, diagnosis, and Glasgow coma scale were all matched to the cohort group.

Diagnosis of VAP

The diagnosis of VAP was made by following the Centers for Disease Control and Prevention criteria (Table 1) [7,8] and confirmed by one of the senior intensive care doctors (CJ).

Intervention

The modified VAP bundle was adopted in this cohort study by increasing the time of intermittent cuff pressure monitoring to every 4 hours (six times a day). We used a hand pressure gauge manometer to monitor and keep the ET cuff pressure at 20–30 cm H_2O (Figure 1). The manometer was directly attached to the ET tube's pilot balloon valve without using a three-way stop cock. If the pressure was less than 20 cm H_2O, we slowly inflated the manometer bulb until it reached a range of 25 to 30 cm H_2O. The time of oral care with 0.12% chlorhexidine was lowered to every 8 hours or three times a day (Table 2). Before feeding, the residual gastric content was always checked, and if it was found to be more than 250 ml, the feeding was temporarily withheld for 2 hours, and then resumed when the residual contents fell below 125 ml. The standard institutional weaning protocol was followed for daily assessment for weaning from mechanical ventilation. The spontaneous breathing trials and eventual extubation were determined by a senior intensive care doctor.

Data Collection and Statistical Analysis

Basic clinical characteristics were recorded. Quantitative data were reported as frequency, percentage, and mean±standard devaition. Statistical analysis using Fischer's exact probability test for comparison between the group. A nonparametric test

Table 1. Diagnosis of VAP [7,8]

Centers for Disease Control and Prevention criteria for diagnosis of VAP
Definition : pneumonia where the patient is on mechanical ventilation for >2 calendar days on the date of the event, with the day of ventilator placement being day 1[a], and the ventilator was in place on the date of the event or the day before.
Imaging test evidence : two or more serial chest imaging test results with at least one of the following New and persistent or progressive and persistent • Infiltrate • Consolidation • Cavitation Note: in patients without underlying pulmonary or cardiac disease (for example respiratory distress syndrome, bronchopulmonary dysplasia, pulmonary edema, or chronic obstructive pulmonary disease), one definitive imaging test result is acceptable.
Sign/symptom For any patient, at least one of the following: • Fever (>38.0°C or >100.4°F) • Leukopenia (≤4,000 WBC/mm^3) or leukocytosis (≥12,000 WBC/mm^3) • For adults ≥70 years old, altered mental status with no other recognized cause And at least two of the following • New onset of purulent sputum or change in the character of sputum, or increased respiratory secretions, or increased suctioning requirements • New onset or worsening cough, or dyspnea, or tachypnea • Rales or bronchial breath sounds • Worsening gas exchange (for example O_2 desaturations (for example PaO_2/FiO_2 ≤240), increased oxygen requirements, or increased ventilator demand)

VAP: ventilator-associated pneumonia; WBC: white blood cell; PaO_2/FiO_2: ratio of arterial oxygen partial pressure to fractional inspired oxygen.
[a]If the ventilator was in place before inpatient admission, the ventilator day count begins with the admission date to the first inpatient location.

(Mann Whitney U-test) was used to compare the duration of using mechanical ventilation.

RESULTS

Patient Demographic Data

During our prospective cohort between November 2018 and June 2020, A total of 291 patients were enrolled in the study, including 145 patients in the cohort group and 146 patients in the matched control group. In terms of sex, age, admission Glasgow coma score, type of neurosurgery, and comorbidity, there were no significant differences between the two groups. However, the control group had a diagnosis of head injury less than the cohort group (41.78% vs. 56.55%, P=0.033) (Table 3).

Table 2. Modification of the VAP bundle

VAP bundle (control group)	Modified VAP bundle (cohort group)
Intermittently check the ET cuff pressure every 6 hours or four times a day	Intermittently check the ET cuff pressure every 4 hours or six times a day
Give oral care with 0.12% chlorhexidine every 6 hours or four times a day	Give oral care with 0.12% chlorhexidine every 8 hours or three times a day

VAP: ventilator-associated pneumonia; ET: endotracheal tube.

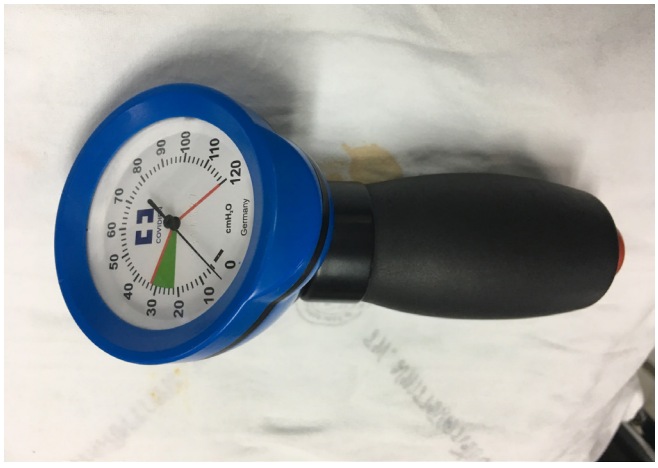

Figure 1. Hand pressure gauge manometer.

Outcomes

VAP was found in nine patients in control group but just one patient in cohort group. When compared to control group, the rate of VAP was considerably low in cohort group (0.88/1,000 vs. 6.84/1,000 ventilator days, P=0.036). Nevertheless, the rates of re-intubation, the day of intubation, and the length of stay were similar in both groups (Table 4).

DISCUSSION

VAP is a serious hospital-acquired infection that is frequently found in intensive care units. In critically ill neurosurgical patients, it has been associated with recovery and prognosis [9,10]. According to Triamvisit et al. [4], the incidence of VAP in the neurosurgical intensive care unit ranged from 7.7 to 27.8 per 1,000 ventilator days. Due to the lack of their normal protective cough mechanism and the reflux of their residual stomach content, intubated patients usually accumulate both normal and abnormal secretion above the ET cuff. The pathogenic microbes are expected to accumulate and proliferate in this secretion, and micro- or macro-aspiration of this secretion

Table 3. Characteristics of Patients between control group and cohort group

Characteristics	Control group (n=146)	Cohort group (n=145)	P-value
Gender			0.092
Male	82 (56.16)	96 (66.21)	
Female	64 (43.84)	49 (33.79)	
Age (yr)	52±16	52±16	0.803
Admission Glasgow coma score	7.79±2.67	7.80±2.77	0.969
Diagnosis			
Head injury	61 (41.78)	82 (56.55)	0.033[a]
Hemorrhagic stroke	42 (28.77)	33 (22.76)	
Brain tumor	30 (20.55)	16 (11.03)	
Infection	5 (3.42)	2 (1.38)	
Others	8 (5.48)	12 (8.28)	
Type of neurosurgery			0.149
No neurosurgery	17 (11.64)	34 (23.45)	
Craniotomy	69 (47.26)	67 (46.21)	
Ventriculostomy	21 (14.38)	18 (12.41)	
Craniectomy	11 (7.53)	6 (4.14)	
Burr hole	8 (5.48)	4 (2.75)	
Ventriculoperitoneal shunt	8 (5.48)	5 (3.45)	
Others surgery	12 (8.22)	11 (7.59)	
Comorbidity			0.811
No	86 (58.90)		
1 disease	36 (24.66)		
≥2 diseases	24 (16.44)		

Values are prsented as number (%) or mean±standard devaition.
[a]P<0.05.

Table 4. VAP, re-intubation, ventilator days, and LOS between control group and cohort group

Variable	Control group (n=146)	Cohort group (n=145)	P-value
VAP			0.019[a]
Yes	9 (6.16)	1 (0.69)	
No	137 (93.84)	144 (99.31)	
VAP/1,000 ventilator days	6.84	0.88	0.036[a]
Re-intubation			0.712
Yes	15 (10.27)	17 (11.72)	
No	131 (89.73)	128 (88.28)	
Ventilatorday	9.01±8.75	7.72±7.33	0.513
Percentile (25th, 50th, 75th)	3, 6, 12	3, 5, 9	
LOS (day)	15.42±14.02	11.88±9.67	0.217
Percentile (25th, 50th, 75th)	6, 11, 20	5, 9, 17	

Values are prsented as number (%) or mean±standard devaition.
VAP: ventilator-associated pneumonia; LOS: length of stay.
[a]P<0.05.

into the patient's lower respiratory tract can result in VAP [11-13]. As a result, any preventive measures to prevent VAP are mandatory in every mechanically ventilated patient.

In our institution, VAP bundle care (Suandok Model) was implemented in 2016 and its effectiveness was reported [4,14,15]. As previously stated, the VAP bundle includes two critical components: ET cuff pressure monitoring and oral care [16-20]. Because the ET cuff pressure is affected by several factors including the patient's position or spontaneous loss of pressure over time, it should be monitored and maintained in an appropriate range (20–30 H_2O) to avoid underinflation, which can lead to VAP from microaspiration [6,11,21,22]. The assessment of cuff pressure by palpation of the ET tube pilot balloon is inaccurate in several studies, hence an intermittent or continuous cuff pressure monitoring device should be used [23]. Despite its superiority, the continuous cuff pressure monitoring device is more expensive and less widely available in most intensive care units. Thus, intermittent cuff monitoring with a hand pressure gauge manometer is a more common practice, especially in the hospital with limited resources. Furthermore, most of the VAP bundle guidelines or other studies that use intermittent cuff pressure monitoring techniques did not specifically state the time or frequency of the cuff pressure monitorings.

In this study, we had proved that our modified VAP bundle, which includes increasing the time of intermittent ET cuff pressure monitoring to every 4 hours (six times a day) and reducing the time of oral care to every 8 hours (three times a day), has comparable or even higher efficacy in reducing the incidence rate of VAP than our old VAP bundle (0.88/1,000 vs. 6.84/1,000 ventilator days, P=0.036). The length of stay was also reduced although it did not show statistical significance (11.88 vs. 15.42 days, P=0.217).

Because no study directly reported the VAP rate in patients who received care with intermittent cuff pressure monitoring, so we used indirect evidence in comparison of our results to the others. According to Nseir et al. [11], the VAP rate in the continuous and the intermittent cuff monitoring group was 9.8% and 26.2%, respectively, while the incidence rate of VAP was 22 per 1,000 ventilator days in the intermittent cuff monitoring group, which is much higher than our result. Similar to Lorente et al. [5], they reported a lower VAP rate in the continuous and the intermittent cuff monitoring group (22.0% vs. 11.2%, P=0.02). Additionally, his study showed the benefit of using an ET with a small-bore lumen for subglottic secretion

drainage. In a series of 144 traumatic brain injury patients, Jovanovic et al. [24] reported the VAP rate that as high as 49.7%. This appears to be in contrast to our findings, which showed the VAP rate of only 0.69% after the modified VAP bundle was implemented.

Regarding oral care, a meta-analysis has shown that oral care with 0.12% chlorhexidine had the best efficacy, in terms of its cost, adverse reactions, and drug resistance for preventing VAP [25-27] The present study showed that reducing oral care from four to three times a day did not affect the VAP bundle's efficacy. This result was similar to findings from other studies, in which the frequency of oral care ranges from two to four times a day [20,28-31]. An unreported survey of our nursing staff yielded a favorable response in terms of reduced manpower and a cost savings. However, the reason why three times a day oral care is sufficient for lowering VAP remains unknown. Therefore, a quantitative comparison of the amount of microorganisms accumulated in oral or subglottic secretion should be investigated further.

Our study, however, has several limitations, including the following: (1) The historical control group may be subject to selection bias and non-compliance, (2) the results in this study can not extrapolate that our intermittent cuff monitoring technique is as effective as continuous pressure monitoring, (3) the surprisingly low VAP rate in the cohort group could be explained by the rigorous policy of following the modified VAP bundle, (4) the cuff pressure should be measured by trained personnel, and the manometer should be re-calibrated regularly, (5) the period of cuff under-inflations was not documented in our study, which could lead to overclaiming results and finally, although, we purpose that our modified VAP bundle has acceptable efficacy and could be a viable option for a hospital with limited resources, a randomized controlled trial that directly comparing continuous cuff monitoring to modified VAP bundle should be done if possible in the future.

In critically ill neurosurgical patients, the modified VAP bundle has been shown to reduce the VAP rate. In hospitals with limited resources, it can be used as an alternative to continuous cuff pressure monitoring. Further study is needed to compare its efficacy to continuous cuff monitoring.

CONFLICT OF INTEREST

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

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Association of vitamin D deficiency with COVID-19 severity and mortality in Iranian people: a prospective observational study

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Background: As the coronavirus disease 2019 (COVID-19) pandemic continues to escalate, it is important to identify the prognostic factors related to increased mortality and disease severity. To assess the possible associations of vitamin D level with disease severity and survival, we studied 248 hospitalized COVID-19 patients in a single center in a prospective observational study from October 2020 to May 2021 in Tehran, Iran.

Methods: Patients who had a record of their 25-hydroxyvitamin D level measured in the previous year before testing positive with COVID-19 were included. Serum 25-hydroxyvitamin D level was measured upon admission in COVID-19 patients. The associations between clinical outcomes of patients and 25-hydroxyvitamin D level were assessed by adjusting for potential confounders and estimating a multivariate logistic regression model.

Results: The median (interquartile range) age of patients was 60 years (44–74 years), and 53% were male. The median serum 25-hydroxyvitamin D level prior to admission decreased with increasing COVID-19 severity (P=0.009). Similar findings were obtained when comparing median serum 25-hydroxyvitamin D on admission between moderate and severe patients (P=0.014). A univariate logistic regression model showed that vitamin D deficiency prior to COVID-19 was associated with a significant increase in the odds of mortality (odds ratio, 2.01; P=0.041). The multivariate Cox model showed that vitamin D deficiency on admission was associated with a significant increase in risk for mortality (hazard ratio, 2.35; P=0.019).

Conclusions: Based on our results, it is likely that deficient vitamin D status is associated with increased mortality in COVID-19 patients. Thus, evaluating vitamin D level in COVID-19 patients is warranted.

Key Words: 25-hydroxyvitamin D; COVID-19; critical care outcomes; SARS-CoV-2

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INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in late 2019, and rapidly reached pandemic levels in 2020, resulting in more than 3,000,000 deaths worldwide [1]. The ongoing COVID-19 pandem-

ic poses major challenges to healthcare systems globally. The clinical presentation of COVID-19 encompasses varied symptoms ranging from asymptomatic, mild to severe illness, including death [2]. To date, elucidating the mechanisms of this variability is crucial to determining the prognostic factors related to the higher mortality and disease severity.

Vitamin D deficiency and insufficiency are highly prevalent and affect almost one billion children and adults worldwide [3]. Beyond the established connection between vitamin D deficiency and mineral homeostasis, 1,25-dihydroxyvitamin D3, the active form of vitamin D, is a pluripotent hormone and key modulator of both innate and adaptive immunity [4]. One review showed that vitamin D has modulatory and regulatory roles in the risk of respiratory viral infections [5], but its causal role in COVID-19 infection is not known. The anti-inflammatory effects of vitamin D and its inhibitory role in the renin-angiotensin system could control immunity and oxidative reactions against COVID-19 infection or progression [6]. Additionally, evidence shows a possible immunological role of vitamin D that can lead to an increase in cellular immunity by inducing antimicrobial peptides [7]. These peptides, such as cathelicidin, destroy pathogens by disrupting their cellular membranes [8,9]. Epidemiological studies have shown that vitamin D-deficient populations have a higher prevalence of COVID-19 [10]. Two recent meta-analyses indicated a positive association of vitamin D deficiency with increased risk of COVID-19 infection [11] and severity [12].

A growing body of evidence supports that vitamin D deficiency aggravates COVID-19. However, the understanding is limited and inconsistent. Therefore, the current study had two main objectives. First, to present the association of vitamin D status prior to COVID-19 infection with disease severity and survival in COVID-19 hospitalized patients. Second, to determine the possible association between admission serum level of vitamin D and COVID-19 severity, including mortality. We hypothesized that patients with previous vitamin D deficiency were deficient at COVID-19 diagnosis.

MATERIALS AND METHODS

The study was carried out in accordance with the Declaration of Helsinki and its subsequent amendments. It was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (No. IR.SBMU.RETECH.REC.1399.884). Written informed consent was obtained from all patients prior to inclusion in the study.

KEY MESSAGES

- Vitamin D deficiency was associated with increased mortality in coronavirus disease 2019 (COVID-19) patients.
- Deficient vitamin D status was associated with increased COVID-19 severity.

Study Design and Participants

This single-center, prospective, observational study was conducted at a university-affiliated hospital from October 2020 to May 2021 in Tehran, Iran. A total of 248 patients who met the following criteria was included: hospitalized patients with positive, real-time, polymerase chain reaction (PCR) test results for COVID-19 based on the World Health Organization interim guidance [13] and chest computed tomography (CT); age 18 years or older; presence of clinical symptoms leading to hospitalization according to the national protocol that included patients with moderate and severe conditions (respiratory rate [RR] >30 times/min, room-air oxygen saturation <93%, ratio of arterial oxygen partial pressure to fractional inspired oxygen [PaO_2/FiO_2] <300 mm Hg); and patients who had a 25-hydroxyvitamin D level measured in the year prior to testing positive for COVID-19. Exclusion criteria were as follows: pregnancy; current breastfeeding; under vitamin D treatment at three months before COVID-19; death or discharge within 24 hours of hospital admission; transfer from another hospital; and end-stage renal disease, end-stage liver disease, and/or parathyroid disease on admission.

Measurements

Data on demographic features, past medical history, clinical symptoms, and clinical outcomes were collected using a checklist. Participants were asked to submit their most recent vitamin D level within one year before their first positive COVID-19 test. Laboratory assessments consisted of complete blood count, serum 25-hydroxycholecalciferol, and C-reactive protein (CRP) measured within 24 hours of hospital admission. Venous blood was drawn in the morning from an antecubital vein. Blood samples were collected in ethylenediaminetetraacetic acid (EDTA)-containing tubes and kept at room temperature for 15–30 minutes. Plasma was centrifuged (3,000 rpm) for 10 minutes at 4°C. Consequently, serum samples obtained were stored at –20°C until laboratory evaluation.

Serum 25-hydroxyvitamin D concentration was measured with the enzyme-linked immunosorbent assay (ELISA) method using a Monobind kit (Monobind Inc., Lake Forest, CA, USA), based on the kit instructions. We categorized serum 25- hydroxycholecalciferol level as deficient when <20 ng/ml and 1,25-dihydroxycholecalciferol level when <18 pg/ml. Vitamin D level ≥20 ng/ml or ≥18 pg/ml was categorized as not deficient [14]. The D-dimer and CRP levels were measured by chemiluminescent immunoassay and immunoturbidimetric assay, respectively. Severe COVID-19 was defined as any one of the following criteria: RR ≥30 breaths/min, PaO_2/FIO_2 ratio <300 mm Hg, arterial blood oxygen saturation (SaO_2) ≤93% in the resting state, and/or lung infiltrates in >50% of the lung field within 24–48 hours from onset of symptoms [15].

Statistical Analysis

Statistical analysis was performed using IBM SPSS ver. 20.0 (IBM Corp., Armonk, NY, USA). Differences were defined as statistically significant at P<0.05. All P-values were considered two-tailed. Kolmogorov-Smirnov test, histogram, and Q-Q plot were used to verify the normal distribution of continuous variables. Quantitative data were expressed as median (Q1–Q3) and qualitative data as number (%). The differences in distribution of categorical variables were analyzed using chi-square test, whereas the Mann-Whitney test was performed to assess differences in the distribution of non-normal variables.

To determine the relationship between serum level 25-hydroxyvitamin D deficiency prior to COVID-19 and clinical outcome (death vs. discharge), univariate and multivariate logistic regression models were performed. Odds ratio (OR) and 95% confidence interval (CI) were calculated to show the intensity and direction of the relationship. Eventually, considering "death" as the event and "time to death/discharge" as event time, survival and proportional hazards Cox regression analyses were used to investigate the effect of admission 25-hydroxyvitamin D deficiency on the hazard ratio (HR) of death in patients with COVID-19 in univariate and multivariate models. The following variables were adjusted in the second model of both regressions: body mass index, sex, age, COVID-19 severity, CRP, and number of comorbidities related to vitamin D metabolism and/or COVID-19, including diabetes, chronic kidney disease, depression, hypertension, chronic pulmonary disease, pulmonary circulation disorders, liver disease, and immunosuppression.

RESULTS

During the study period, 248 patients provided a record of vitamin D level measured within the previous year prior to testing positive for COVID-19. Figure 1 shows a study flow diagram. The median (interquartile range) age was 60 years (44–74 years), and there were 132 male participants (53%). Among the total patients, 59 (23.8%) did not have any comorbidity, and 109 (44%) and 133 (53.6%) had vitamin D deficiency within one year before and after COVID-19 testing, respectively. Demographic and clinical characteristics of participants are listed in Table 1 including vitamin D classification prior to COVID-19 and at admission. Study participants differed in terms of age, severity of COVID-19, and D-dimer level across the two vitamin D groups. There were statistically significant differences for mortality between the vitamin D deficient before COVID-19 group (22.9%) and the vitamin D non-deficient group (12.9%) (P=0.039). Similar results were obtained between the vitamin D deficient at admission group (22.6%) and the vitamin D non-deficient group (11.3%) (P=0.020).

Among the 109 patients who were vitamin D deficient one year before admission, 42 were in the sufficient group at the time of COVID-19 diagnosis, and 67 remained vitamin D deficient. Mortality was significantly higher in vitamin D deficient patients (21/67, 31%) than in the sufficient group (4/42, 9.5%) (P=0.008). The hospital length of stay was significantly shorter in the sufficient group patients than in the deficient group (7 [5–12.2] vs. 12 [6–15], P=0.018).

Figure 2 depicts the comparison of the vitamin D level measured between moderate and severe COVID-19 patients at 1 year before diagnosis and at admission. Median serum 25-hydroxyvitamin D measured one year before COVID-19 decreased with increasing COVID-19 severity (22 [15–32] vs. 19 [11–26], P=0.009). Similar results were obtained when comparing median serum 25-hydroxyvitamin D at admission between moderate and severe patients (20 [12–25]) vs. 15 [8–25], P=0.014).

Tables 2 and 3 show the odds and HRs of death by 25-hydroxyvitamin D deficiency in patients prior to COVID-19 infection and at admission, respectively. Univariate logistic regression showed that patients with vitamin D deficiency (<20 ng/ml) at 1 year before COVID-19 had significantly higher odds of death (OR, 2.01; 95% CI, 1.03–3.90; P=0.041). However, after adjustment for confounders, the association was not significant (OR, 1.94; 95% CI, 0.94–4.01; P=0.074). In both univariate and multivariate Cox models, vitamin D deficient sta-

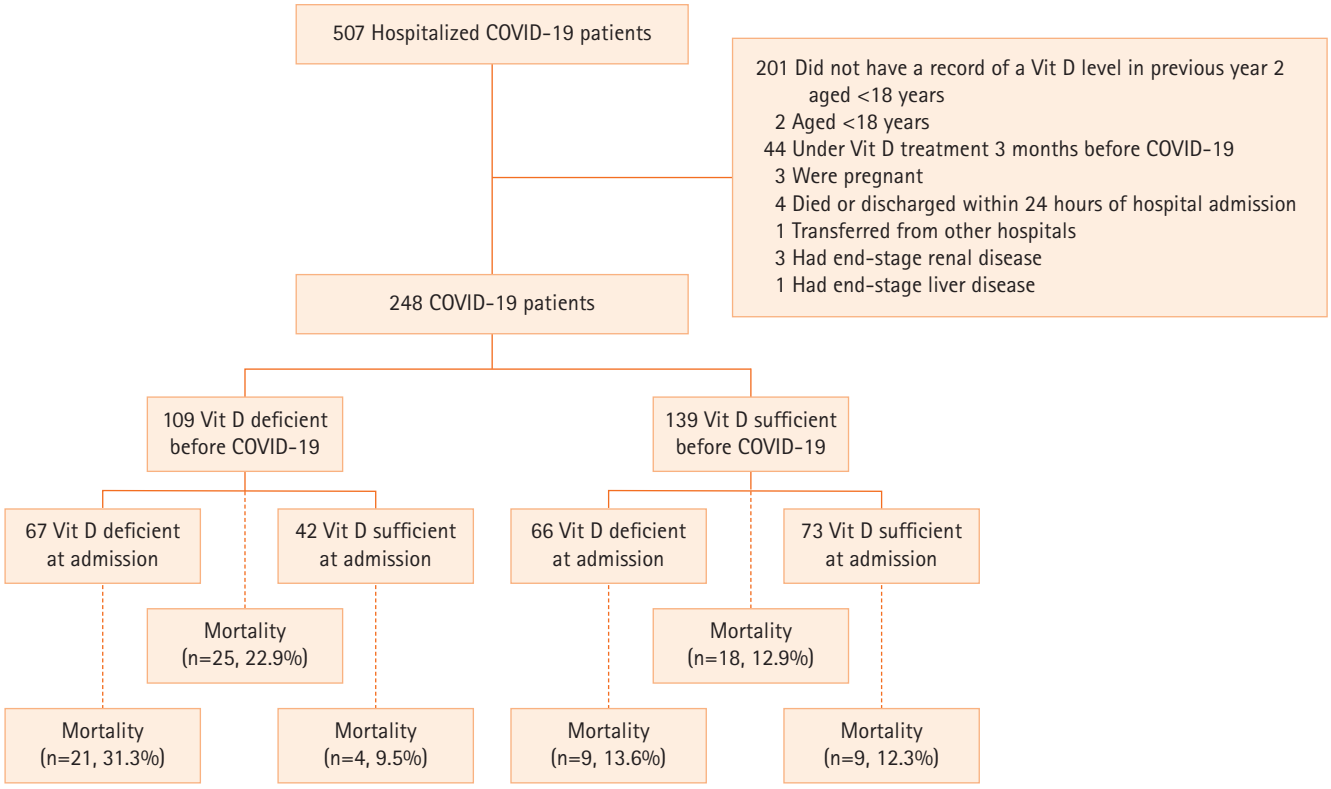

Figure 1. Flowchart of patient selection and mortality based on vitamin D (Vit D) status before and after coronavirus disease 2019 (COVID-19).

tus at admission increased the HR of death (HR, 2.18; 95% CI, 1.12–4.26; P=0.023 and HR, 2.35; 95% CI, 1.15–4.78; P=0.019, respectively).

DISCUSSION

This study was designed to determine the association of vitamin D status prior to exposure to COVID-19 with disease severity and survival and to determine the association of admission serum level of vitamin D with disease severity and mortality in COVID-19 hospitalized patients. Our main finding is that COVID-19 patients with vitamin D deficiency upon admission were at substantially higher risk of mortality than were COVID-19 patients with sufficient levels. However, this association was not significant in patients with deficient vitamin D level before COVID-19 testing compared with patients with sufficient vitamin D status.

The advent of COVID-19 created awareness among researchers regarding the role of vitamin D in disease severity. One of the first ecological studies showed a negative correlation between vitamin D level and number of COVID-19 cases and mortality caused by this disease in various European countries [16]. D'Avolio et al. [17] reported that 25-hydroxyvitamin D concentration was lower in patients with positive PCR for SARS-CoV-2 compared with patients that had negative PCR. Meltzer et al. [18] found that deficient vitamin D status was associated with increased COVID-19 risk in a Chicago population. Our results support two recent meta-analyses that show a positive association of vitamin D deficiency with severity of COVID-19 [12] and with increased risk of COVID-19 infection [11]. In line with our result, Luo et al. [6] found a significant association between vitamin D deficiency and COVID-19 severity in a Chinese population. Furthermore, Radujkovic et al. [19] demonstrated an association between vitamin D deficiency and severity of and mortality from COVID-19 in a German population. However, Tehrani et al. [20] showed no statistical difference in vitamin D level between Iranian COVID-19 patients who died at the hospital and those who improved. Furthermore, Murai et al. [21], in a double-blind, randomized, placebo-controlled trial, demonstrated that a single high dose of vitamin D3 did not significantly improve clinical outcomes in patients with moderate to severe COVID-19.

In our study, most of the patients with previous vitamin D deficiency remained deficient at COVID-19 diagnosis. Patients

Table 1. The demographic, clinical, and paraclinical characteristics of overall patients with COVID-19 and stratified by vitamin D level

Variable	Overall	1 Year before COVID-19 positive test			At admission		
		Vitamin D classification			Vitamin D classification		
		<20 ng/mL	≥20 ng/mL	P-value	<20 ng/mL	≥20 ng/mL	P-value
No. of patients	248	109	139		133	115	
Age (yr)	60 (44–74)	65 (49–75)	55 (38–70)	0.002[a,b]	61 (47–75)	58 (36–70)	0.033[a,b]
Sex				0.439[c]			0.957[c]
Male	132 (53.2)	55 (50.5)	77 (55.4)		71 (53.4)	61 (53)	
Female	116 (46.8)	54 (49.5)	62 (44.6)		62 (46.6)	54 (47)	
Educational level				0.461[c]			0.757[c]
Primary/secondary school	38 (15.3)	20 (18.3)	18 (12.9)		20 (15)	18 (15.7)	
Bachelor's degree	167 (67.3)	72 (66.1)	95 (68.3)		92 (69.2)	75 (65.2)	
Master's/doctoral degree	43 (17.3)	17 (15.6)	26 (18.7)		21 (15.8)	22 (19.1)	
Severity of COVID-19				0.006[a,c]			0.018[a,c]
Moderate	162 (65.3)	61 (56)	101 (72.7)		78 (58.6)	84 (73)	
Severe	86 (34.7)	48 (44)	38 (27.3)		55 (41.4)	31 (27)	
Body mass index (kg/m^2)	27.5 (25–33.5)	26.1 (25–33.2)	28 (25–33.8)	0.156[b]	27.2 (25–33.8)	27.5 (25–32.7)	0.897[b]
Body mass index ≥30 kg/m^2	93 (37.5)	35 (32.1)	58 (41.7)	0.121[c]	52 (39.1)	41 (35.7)	0.576[c]
Comorbidity							
Diabetes	55 (22.2)	28 (25.7)	27 (19.4)	0.239[c]	32 (24.1)	23 (20)	0.443[c]
Hypertension	83 (33.5)	41 (37.6)	42 (30.2)	0.220[c]	42 (31.6)	41 (35.7)	0.498[c]
Pulmonary circulation disorder	17 (6.9)	9 (8.3)	8 (5.8)	0.439[c]	8 (6)	9 (7.8)	0.574[c]
Chronic pulmonary disease	63 (25.4)	25 (22.9)	38 (27.3)	0.429[c]	36 (27.1)	27 (23.5)	0.517[c]
Chronic kidney disease	50 (20.2)	25 (22.9)	25 (18)	0.335[c]	28 (21.1)	22 (19.1)	0.707[c]
Liver disease	22 (8.9)	10 (9.2)	12 (8.6)	0.882[c]	9 (6.8)	13 (11.3)	0.210[c]
Immunocompromised state	58 (23.4)	30 (27.5)	28 (20.1)	0.173[c]	26 (19.5)	32 (27.8)	0.125[c]
Depression	49 (19.8)	27 (24.8)	22 (15.8)	0.079[c]	31 (23.3)	18 (15.7)	0.131[c]
Laboratory data							
Total leucocyte count	7,856 (5,856–11,165)	8,002 (5,929–12,183)	7,850 (5,854–10,901)	0.403[b]	8,502 (5,856–12,735)	7,660 (5,803–10,012)	0.160[b]
Lymphocyte count	22.8 (17–31.5)	22.8 (17–31.7)	22.8 (17–30.8)	0.877[b]	23.3 (16.7–35.6)	22.3 (17–29.1)	0.464[b]
CRP level (mg/dl)	4.50 (3.35–6.08)	5.01 (3.66–6.31)	4.40 (3.21–6.01)	0.052[b]	5.02 (4.01–6.31)	4.03 (2.51–5.90)	0.001[a,b]
D-dimer (ng/ml)	854 (522–1,240)	874 (521–1,499)	852 (525–987)	0.027[a,b]	874 (755–1,437)	854 (485–984)	0.002[a,b]
O_2 saturation (%)	88 (85–89)	87 (85–89)	88 (87–89)	0.066[b]	88 (86–89)	87 (85–90)	0.144[b]
Clinical outcome							
Mortality	43 (17.3)	25 (22.9)	18 (12.9)	0.039[a,c]	30 (22.6)	13 (11.3)	0.020[a,c]
Hospital length of stay (day)	9 (7–14)	9 (5–14)	9 (7–15)	0.062[b]	9 (7–14)	8 (6–14)	0.197[b]

Values are presented as median (interquartile range) or number (%).
COVID-19: coronavirus disease 2019; CRP: C-reactive protein.
[a]Statistically significant; [b]Mann-Whitney test; [c]Chi-square test.

whose vitamin D status changed from deficient to sufficient had better clinical outcomes. Moreover, vitamin D deficiency was associated with either COVID-19 severity or linked mortality. Therefore, our findings suggest that treatment of vitamin D deficiency can prevent COVID-19 death.

Vitamin D has shown not only anti-inflammatory and anti-microbial properties, but also is an immunomodulator. Vitamin D deficiency can augment COVID-19 severity and mortality by triggering a hyperinflammatory state and a cytokine storm. Data show that vitamin D deficiency in COVID-19 patients presents significantly higher levels of inflammatory and coagulation biomarkers including CRP, D-dimer, interleukin-6, tumor necrosis factor-α, fibrinogen, and ferritin [22-24]. Furthermore, vitamin D has been implicated to negatively reg-

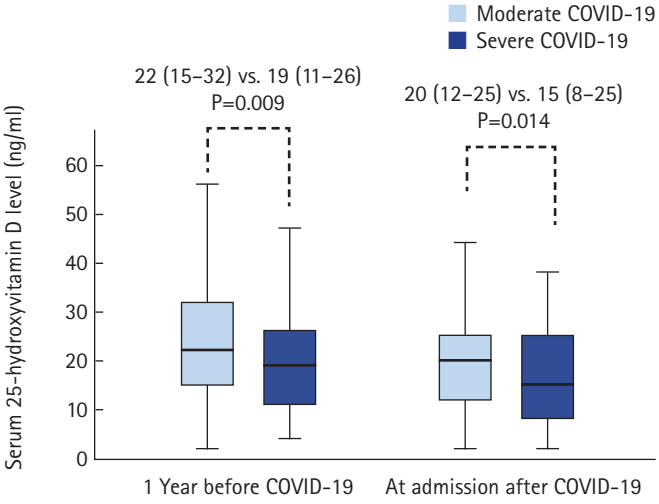

Figure 2. Median serum 25-hydroxyvitamin D level according to coronavirus disease 2019 (COVID-19) severity category. Values are presented as median (interquartile range). P-values were calculated using the Mann-Whitney U-test.

ulate the renin-angiotensin system. Cell entry of SARS-CoV-2 depends on binding of angiotensin-converting enzyme 2 (ACE2) as a receptor. Vitamin D inhibits the synthesis of renin and increases ACE2 expression and angiotensin (1-7) production in the lung, decreasing the risk of SARS-CoV-2 infection and prevent COVID-19 symptoms [24,25].

This study had several limitations. First, vitamin D deficiency can be associated closely with a range of chronic diseases or behavioral characteristics that possibly increase COVID-19 risk. Second, the data were from those who had a 25- hydroxyvitamin D level measured in the year before infection with COVID-19 and were not treated with vitamin D. Third, the study was conducted in a single center located in Tehran, an area with a high prevalence of vitamin D deficiency. Fourth, the study might be prone to selection bias; if vitamin D deficiency testing was more likely in COVID-19 patients than non-infected patients, this might introduce a selection bias.

Table 2. Univariate and multivariate logistic regression analyses of mortality affected by 25(OH)D deficiency at admission in patients with COVID-19[a]

Variable	Dead	Univariate analysis		Multivariate analysis	
		OR (95% CI)	P-value	OR (95% CI)	P-value
Age (yr)	67 (45–75)	0.98 (0.96–1.01)	0.115	0.99 (0.97–1.02)	0.542
Male	21 (48.8)	1.24 (0.64–2.39)	0.526	1.20 (0.59–2.46)	0.598
BMI (kg/m^2)	26.1 (25.1–34.7)	0.98 (0.93–1.03)	0.395	0.97 (0.92–1.02)	0.233
CRP (mg/dl)	4.3 (3.3–5.6)	1.12 (0.93–1.34)	0.249	1.19 (0.97–1.47)	0.103
Severe COVID-19	25 (58.1)	3.28 (1.67–6.45)	0.001	2.99 (1.46–6.09)	0.003
Number of comorbidities	1 (1–3)	1.07 (0.83–1.38)	0.619	1.13 (0.86–1.48)	0.387
25(OH)D prior to COVID-19 deficiency	25 (58.1)	2.01 (1.03–3.90)	0.041	1.94 (0.94–4.01)	0.074

Values are presented as median (interquartile range) or number (%) unless otherwise indicated.
25(OH)D: 25-hydroxyvitamin D; COVID-19: coronavirus disease 2019; OR: odds ratio; CI: confidence interval; BMI: body mass index; CRP: C-reactive protein.
[a]Multivariable analyses were conducted using logistic regression models utilizing the simultaneous method.

Table 3. Univariate and multivariate Cox regression analyses of mortality affected by admission 25(OH)D deficiency in patients with COVID-19[a]

Variable	Dead	Univariate analysis		Multivariate analysis	
		HR (95% CI)	P-value	HR (95% CI)	P-value
Age (yr)	67 (45–75)	1.02 (1.01–1.04)	0.031	1.01 (0.99–1.03)	0.355
Male	21 (48.8)	1.23 (0.68–2.25)	0.491	1.12 (0.59–2.14)	0.721
BMI (kg/m^2)	26.1 (25.1–34.7)	1.03 (0.99–1.08)	0.156	1.03 (0.98–1.08)	0.197
CRP (mg/dl)	4.3 (3.3–5.6)	0.88 (0.74–1.03)	0.117	0.80 (0.66–0.97)	0.021
Severe COVID-19	25 (58.1)	3.45 (1.79–6.65)	<0.001	2.90 (1.46–5.77)	0.002
Number of comorbidities	1 (1–3)	0.94 (0.74–1.18)	0.574	1.03 (0.81–1.31)	0.802
25(OH)D at admission deficiency	30.0 (69.8)	2.18 (1.12–4.26)	0.023	2.35 (1.15–4.78)	0.019

Values are presented as median (interquartile range) or number (%) unless otherwise indicated.
25(OH)D: 25-hydroxyvitamin D; COVID-19: coronavirus disease 2019; HR: hazard ratio; CI: confidence interval; BMI: body mass index; CRP: C-reactive protein.
[a]Multivariable analyses were conducted using Cox regression models utilizing the simultaneous method.

Finally, the time difference between infection and admission was not taken into consideration; the quantitative variables were measured only upon admission.

In conclusion, the findings of this study provide evidence that vitamin D could be a factor in improving clinical outcome in COVID-19 patients. These findings have implications for future randomized clinical trials to assess the effects of vitamin D supplementation on clinical outcome in COVID-19 patients with vitamin D deficiency.

CONFLICT OF INTEREST

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

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Conceptualization: AF, SHA, GE. Data curation: GE, SM. Formal analysis: SHA, GE, MN. Funding acquisition: AF, SHA, GE, MN. Methodology: AF, SHA, GE, SM. Project administration: GE. Visualization: AF, MN. Writing–original draft: AF, SHA, GE. Writing–review & editing: all authors.

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COVID-19–induced acute kidney injury in critically ill patients: epidemiology, risk factors, and outcome

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Background: The kidney represents a potential target for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Clinical data about acute kidney injury (AKI) during SARS-CoV-2 infection are lacking. We aimed to investigate the proportion, risk factors, and prognosis of AKI in critical patients affected with SARS-CoV-2.

Methods: A case/control study was conducted in two intensive care units of a tertiary teaching hospital.

Results: Among 109 patients, 75 were male (69%) with median age at 64 years and 48 (44%) developed AKI within 4 days (interquartile range [IQR], 1–9). Of them, 11 (23%), 9 (19%), and 28 (58%) were classified as stage 1, 2, and 3, respectively. AKI patients were older and presented more sepsis, acute respiratory distress syndrome, and rhabdomyolysis; higher initial urea and creatinine; more marked inflammatory syndrome and hematological disorders; and required more mechanical ventilation and vasopressors. An elevated D-dimers level (odds ratio [OR], 12.83; 95% confidence interval [CI], 1.9–85) was an independent factor of AKI. Sepsis was near to significance (OR, 5.22; 95% CI, 0.94–28; P=0.058). AKI was independently related to mortality (OR, 6.8; 95% CI, 1.49–105) and significantly reduced the survival (14.7 days; IQR, 12-17 vs. 19.9 days; IQR, 17-22.7; P=0.011) in AKI and no AKI group respectively. Hypoxemia with the ratio of the arterial partial pressure of oxygen and the inspiratory concentration of oxygen <70, and vasopressors were identified as mortality factors.

Conclusions: AKI occurred in almost half the studied patients and significantly worsened their prognosis. A high D-dimers level and sepsis contributed significantly to its development.

Key Words: acute kidney injury; coronavirus disease 2019; mechanical ventilation; mortality

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INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) affects multiple organ systems and imparts significant morbidity and mortality [1]. Approximately 5% to 14% of patients affected with SARS-CoV-2 will become critically ill [2-4]. While coronavirus disease 2019 (COVID-19) generally begins as a respiratory tract infection, it can damage any organ system. Thus, to improve outcomes, clinicians should search actively for multi-organ involvement to guide appropriate early management [5].

Among affected organs, the kidney is particularly susceptible to COVID-19. Indeed, SARS-CoV-2 has been shown to share the same functional receptor, angiotensin-converting enzyme 2 (ACE2), with a wide variety of organs (such as lung, heart, kidney) [6]. SARS-CoV-2 initiates its infection process by binding to functional receptors on the membrane of a host cell. Postmortem examination of COVID-19 patients revealed varying degrees of acute tubular necrosis, lymphocytic infiltration, and viral RNA, suggesting direct invasion of kidney tubules [7]. In addition to direct kidney damage by the virus, acute kidney injury (AKI) can occur through several proposed mechanisms including acute tubular necrosis induced by sepsis, hypoxia, hypoperfusion, rhabdomyolysis, nephrotoxic drugs, etc.

In critically ill patients, AKI is a common complication of COVID-19 infection, occurring in 23% to 43% of cases [8-10], and was correlated with poor clinical outcomes [11]. At present, information regarding the epidemiology and the clinical correlates, prognosis, and determinants of AKI in patients with COVID-19 remain scarce. In this study, we aimed to evaluate the frequency, risk factors, and outcomes of AKI in critically ill patients with confirmed COVID-19.

KEY MESSAGES

- Acute kidney injury (AKI) occurred in 44% of critically ill patients affected with coronavirus disease 2019 (COVID-19).
- A high level of D-dimers and less significance of sepsis were factors related with the development of AKI.
- AKI increased the death risk by 6 and reduced survival by an average of 5 days.
- Elevated D-dimers was the most related factor to COVID-19-induced AKI that should emphasis more the role of micro thrombi and considers further the curative anticoagulation and immunomodulatory treatments.

MATERIALS AND METHODS

Design

This was a retrospective comparative case/control study conducted between September 2020 and December 2020 in two intensive care units (ICUs) designated for critical COVID-19 cases of the tertiary teaching hospital of La Rabta (Tunis, Tunisia). Regarding the two participating units, one was an existing medical ICU of multivalent activity managed by medical intensivists, and the other was a novel unit created especially for the COVID-19 outbreak and managed by anesthetists. The hospitalization capacity was six beds in both units. The Ethics Committee of La Rabta University Hospital approved the study protocol and waived informed consent because of the retrospective and descriptive nature of the study. The principles outlined in the Declaration of Helsinki as revised in 2013 were followed in the study protocol.

Patients

The medical records of all adult patients (>18 years) with laboratory-confirmed COVID-19 who were admitted to the two ICUs during the study period were examined. The SARS-CoV-2 RNA was detected using reverse transcription-polymerase chain reaction for laboratory diagnosis of COVID-19. The samples consisted of nasal swabs or endotracheal aspirate. Patients who met the criteria of critical COVID-19 as defined below were included. The case group included the critical COVID-19 patients who presented with AKI during their ICU stay, and the control group was the critical COVID-19 patients who maintained normal kidney function. Excluded patients were those who did not meet the critical COVID-19 criteria, those whose medical records data were missing, and those with early multi-organ failure (MOF) including AKI.

Therapeutic Management

Standard care was based on oxygen support (invasive or non-invasive) associated with the prone position, corticosteroids (dexamethasone 8 mg/day), anticoagulation, and vitamin supplementation. In our unit, the usual anticoagulation protocol was based on unfractionated heparins and low molecular weight heparin; the dose depended on curative or preventive indication, creatinine clearance, and weight of the patient. For the preventive protocol and creatinine clearance >30 ml/min: if body mass index (BMI) <30 kg/m^2, enoxaparin 0.4 ml/day; if BMI ≥30 kg/m^2, enoxaparin 0.4 ml ×2/day; and if weight >120 kg, enoxaparin 0.6 ml ×2/day. In cases of clearance <30 ml/min: heparin sodium 200 IU/kg/day or calciparin 150 IU/kg/day was administered in two subcutaneous injections. In the presence of confirmed thrombosis (pulmonary embolism or phlebitis), the curative protocol was as follows (patient weight: dose of enoxaparin) 50–59 kg: 0.5 ml ×2/day, 60–69 kg: 0.6 ml ×2/day, 70–79 kg: 0.7 ml ×2/day, 80–89 kg: 0.8 ml ×2/day, 90–99 kg 0.9 ml ×2/day, and weight ≥100 kg: 1 ml ×2/day. If creatinine clearance <30 ml/min, intravenous heparin 3–5 mg/kg/day is administered continuously via electric syringe pump over 24 hours.

Assessed Data

For each patient, we recorded demographics, comorbidities, basic drugs received, clinical features, initial laboratory findings, initial computed tomography (CT) scan data, treatment (respiratory supports, use of medications, and renal replacement therapy (RRT), and clinical outcomes. The daily values of urea and creatinine were recorded. All data were entered into the computerized database for further statistical analysis.

Definitions

A patient affected by COVID-19 was considered critical and required ICU transfer in the presence of respiratory distress (respiratory rate ≥30 times/min plus cyanosis) and the use of oxygen support to maintain oxygen saturation as measured by pulse oximetry (SpO_2) >92%. The oxygen support could be noninvasive including noninvasive ventilation (NIV) and high-flow nasal cannula (HFNC) or invasive with requirement of ventilator support (mechanical ventilation [MV]). Shock and MOF were also considered critical criteria. The oxygen support modality recorded was that used before AKI (either on ICU admission or during hospitalization before AKI).

Sepsis was defined according to the 3rd international consensus (Sepsis-3); i.e., presence of organ dysfunction (identified as an acute change in total Sequential Organ Failure Assessment [SOFA] score ≥2 points), consequent to the infection [12]. To avoid bias, we did not consider sepsis that included AKI at the time of diagnosis. It was only when sepsis preceded AKI that it was analyzed as a risk factor.

The definition and severity staging of AKI were based on the Kidney Disease: Improving Global Outcomes (KDIGO) classification [13] as follows. Stage 1 involves increase in serum creatinine to 1.5–1.9 times baseline odds ratio (OR) >0.3 mg/dl (>26.5 μmol/L) and/or urine output <0.5 ml/kg/hr for 6–12 hours. Stage 2 is increase in serum creatinine to 2.0–2.9 times baseline and/or urine output <0.5 ml/kg/hr for >12 hours. Stage 3 is defined by increase in serum creatinine to 3.0 times baseline, increase in serum creatinine to >4.0 mg/dl (>353.6 μmol/L), initiation of RRT, and/or urine output <0.3 ml/kg/hr for >24 hours, or anuria for >12 hours. For patients without available baseline serum creatinine (bSCr), we estimated bSCr using the modification of diet in renal disease equation: back-estimation formula: serum creatinine=[75/186×(age–0.203)×(0.742 if female)×(1.21 if black)–0.887] as suggested by KDIGO guidelines to estimate bSCr in the absence of prior renal disease [14,15]. In patients with suspected chronic kidney disease, the lowest creatinine measured in the first three days of hospitalization was considered bSCr.

The definition of AKI recovery was based on that of the Acute Disease Quality Initiative 16 workgroup [16]. Rhabdomyolysis was retained if the creatine phosphokinase rate was greater than five times the upper limit of normal. Nephrotoxic drugs are those toxic to the kidney. In our unit, the most prescribed were colistin, aminoglycosides, vancomycin, and iodine contrast agent.

Study Outcomes

We focused mainly on frequency of AKI and its risk factors. We also assessed outcomes of AKI, RRT requirement, and the impact of AKI on mortality in critical COVID-19 patients.

Statistical Analysis

Continuous variables were expressed as the median and interquartile range (IQR) and compared with a nonparametric Mann-Whitney test. Categorical variables were expressed as counts and percentages and compared using a chi-square test or Fisher's exact test as appropriate. The risk factors for AKI and those associated with 28-day mortality were screened with the univariate logistic regression model. The variables with a P-value of 0.2 or less were analyzed with multicollinearity tests to clear interferences and overlaps and were imported into a logistic regression analysis using the entered method. Survival analysis was processed by the Kaplan-Meier curves and compared by the Log-rank test. The significance threshold was set at a two-sided P-value less than 0.05. All statistical analyses were performed using IBM SPSS ver. 20 (IBM Corp., Armonk, NY, USA).

RESULTS

Baseline Characteristics and Proportion of AKI

In the included 109 patients, male gender was predominant (75/34; sex ratio, 2.2), and the median age was 64 years (IQR, 57–71 years). Five of the patients had chronic renal failure. During hospitalization, AKI occurred in 48 patients (44%). Table 1 shows the evaluated parameters in all populations and, for each group, according to presence of AKI. Laboratory and CT scan findings in the table are those collected at ICU admission. The AKI patients were older and had more frequent hypertension, higher severity scores, and more predisposing conditions (such as sepsis, acute respiratory distress syndrome [ARDS], and rhabdomyolysis) and required more frequent MV and vasopressors. Notably, prior use of ACE in-

Table 1. Assessed parameters in all patients according to presence of AKI

Variable	Total population (n=109)	AKI group (n=48)	No AKI group (n=61)	P-value
Age	64 (57–71)	69 (61–77)	60 (55–66)	<0.001
> 60 yr	67 (61.5)	37 (77)	30 (49)	0.003
Sex (male:female)	75:34	33:15	42:19	0.999
BMI	27 (24–31)	27.3 (24.5–30.7)	27 (24–32.5)	0.620
Obesity (BMI >30 kg/m^2)	32 (29.5)	11 (23)	21 (34.5)	0.182
Comorbidity				
Hypertension	56 (51.5)	30 (62.5)	26 (42.6)	0.054
Prior use of ACE inhibitor/A2RB	27 (25)	16 (33.5)	11 (18)	0.071
Diabetes	44 (40)	23 (48)	21 (34.4)	0.175
Chronic renal failure	5 (4.5)	1 (2)	4 (6.5)	0.388
Chronic respiratory failure	20 (18.5)	8 (16.5)	12 (20)	0.804
Cardiomyopathy	18 (16.5)	9 (19)	9 (15)	0.613
Immunocompromised	6 (5.5)	4 (8.3)	2 (3.3)	0.489
Severity score				
APACHE II	10.5 (7–16)	13 (10–18)	9 (6–11)	<0.001
SAPS II	30 (22–40)	38 (31–53)	24 (16–30.7)	<0.001
SOFA	4 (3–9)	7 (4–11)	4 (2–7.5)	0.001
Initial laboratory finding				
Baseline serum urea (g/L)	0.57 (0.39–1.05)	1 (0.71–1.3)	0.45 (0.36–0.56)	<0.001
Baseline creatinine (mg/L)	9 (7–14)	12.5 (9–18.4)	8 (7–10)	<0.001
Minimum P/F ratio	66 (48–93)	60 (46–78)	73 (55–126)	0.110
WBC count (×10^9/L)	12 (8.5–17)	17 (7–21)	10 (4–15)	0.033
Minimum lymphocyte (×10^3/μl)	520 (312–720)	510 (320–760)	550 (302–715)	0.819
Platelet (×10^9/L)	141 (48–238)	134 (33–266)	145 (58–229)	0.772
CRP (mg/L)	199 (98–280)	248 (171–326)	151 (74–242)	0.002
Prothrombin time (%)	60 (45–80)	56 (41–69)	75 (52–86)	0.001
Fibrinogen (g/L)	5.1 (1.7–6.4)	5.5 (4.2–6.9)	2.5 (1.5–6.2)	0.179
D-dimer (μg/L)	1,402 (653–3,881)	2,222 (813–5,109)	905 (598–1,757)	0.002
Lactate (mmol/L)	2.1 (1.6–6)	2.1 (1.7–4)	1.9 (1.6–3.6)	0.448
CT scan lesion extension at admission[a], >50%	33/78 (42)	13/31 (42)	20/47 (42.5)	0.999
Predisposing condition				
Sepsis	49 (45)	35 (73)	14 (23)	<0.001
ARDS	81 (74)	38 (81)	43 (70.5)	0.953
ACP[a]	10/66 (15)	8/29 (27.5)	2/37 (5.4)	0.017
Rhabdomyolysis	21 (19)	14 (29	7 (11.5)	0.086
Vasopressor	60 (55)	40 (84)	20 (33)	<0.001
Nephrotoxic drug	29 (27)	20 (42.5)	9 (15)	0.014
Respiratory support				
Alternation HFNC/NIV	61 (56)	18 (37.5)	43 (70.5)	-
MV	48 (44)	30 (62.5)	18 (29.5)	0.001

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

AKI: acute kidney injury; BMI: body mass index; ACE: angiotensin-converting enzyme; A2RB: angiotensin II receptor blockers; APACHE: Acute Physiology and Chronic Health Evaluation; SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment; P/F ratio: ratio of the arterial partial pressure of oxygen and the inspiratory concentration of oxygen; WBC: white blood cell; CRP: C-reactive protein; CT: computed tomography; ARDS: acute respiratory distress syndrome; ACP: acute cor pulmonale; HFNC: high-flow nasal cannula; NIV: noninvasive ventilation; MV: mechanical ventilation.

[a]CT scan performed in 78 patients and echocardiography in 66 patients.

hibitor or angiotensin II receptor blocker (A2RB) was observed more frequently in the AKI group with P close to significance. Several biological differences were found; both initial urea and creatinine were higher in the AKI group. Moreover, inflammatory and hematological disorders were found more often in the AKI patients.

AKI Characteristics and Risk Factors

Among 48 patients (44%) who developed AKI during hospitalization, 11 (23%), 9 (19%), and 28 (58%) were classified as KDIGO stage 1, 2, and 3, respectively. Eight patients (17%) received RRT (5 in the stage 2 category and 3 in the stage 3 category). AKI occurred within a median of 4 days [1-9].

Age over 60 years, hypertension, prior use of ACE inhibitor/A2RB, diabetes, the ratio of the arterial partial pressure of oxygen and the inspiratory concentration of oxygen (P/F ratio) <70, C-reactive protein (CRP) >200 mg/L, fibrinogen >5 g/L, D-dimers >1400 μg/L, sepsis, rhabdomyolysis, MV, vasopressors, and nephrotoxic drugs were the factors introduced in the multivariate analysis. Conditions and factors included in the analysis were only considered if they preceded AKI. In the results, elevated D-dimers was an independent factor significantly associated with AKI in critical COVID-19 patients, with OR, 12.83; 95% CI, 1.9–85. Sepsis tended to be a related factor with OR near significance (OR, 5.22; 95% CI, 0.94–28; P=0.058). These findings are shown in Table 2.

Table 2. Factors associated with AKI in multivariate analysis

Variable	Odds ratio	P-value
Age > 60 yr	1.35	0.320
Hypertension	1.58	0.612
Prior use of ACE inhibitor/A2RB	1.25	0.124
Diabetes	1.55	0.402
P/F ratio <70	2.54	0.154
CRP >200 mg/L	2.21	0.140
Fibrinogen >5 g/L	3.03	0.115
D-dimers >1,400 μg/L	12.83 (1.9–85)[a]	0.008
Sepsis	5.22 (0.94–28)[a]	0.058
Rhabdomyolysis	6.53	0.072
MV	4.30	0.124
Vasopressor	1.82	0.466
Nephrotoxic drug	4.26	0.080

AKI: acute kidney injury; ACE: angiotensin-Converting enzyme; A2RB: angiotensin II receptor blockers; P/F ratio: the ratio of the arterial partial pressure of oxygen and the inspiratory concentration of oxygen; CRP: C-reactive protein; MV: mechanical ventilation.
[a]95% confidence interval.

Outcomes

Renal function improved in only three patients (6.25%), who were classified as KDIGO stage 1. Ventilation days and ICU stay were similar between the two groups (6 [3–8] vs. 4 [2–8], P=0.12 and 7 [5–10] vs. 8 [4–15], P=0.59) in patients with AKI and those without, respectively. Of 109 patients, 65 showed deceased mortality within 28 days of ICU admission (ICU 28-day mortality, 59; 6%), which was significantly higher in AKI patients (41/48 [85%] vs. 24/61 [39.4%], P<0.001). All patients classified as KDIGO 3 died (Table 3).

In non-survivor patients, AKI, hypoxemia, sepsis, vasopressors, and MV requirements were more frequent than in survivors. Contrary to common findings, there were fewer obese subjects among deceased patients (Table 3). In multivariate analysis, AKI, severe hypoxemia (P/F ratio <70), and vasopressors were associated with mortality (Table 3).

Survival Analysis

When AKI occurred in critical COVID-19 patients, it decreased the survival delay time by an average of 5 days (14.7 days; IQR, 12-17 vs. 19.9 days; IQR, 17-22.7; P=0.011) in AKI group and no AKI group respectively, as shown in Figure 1.

DISCUSSION

We showed that, among 109 critical COVID-19 patients, 48 (44%) developed AKI that was mostly classified as KDIGO 3. At baseline, multiple clinical and biological differences between the AKI group and no AKI group were observed. Concerning the association with AKI, elevated D-dimers was the most significant independent factor. Sepsis was related closely to AKI. Overall, the 28-day mortality was poor at 59.6% and was higher in AKI patients (85%). This complication was related to mortality (OR, 6.8; 95% CI, 1.49–105) and significantly reduced survival.

Descriptive Epidemiology

Compared to other reported figures, our proportion of patients with AKI was high at 44%. Indeed, AKI occurred in 0.5%–15% of hospitalized patients affected with SARS-CoV-2 [17] and in up to 23% of COVID ICU patients [8,9]. Before emergence of COVID, Panitchote et al. [18] reported an incidence rate of 68.3% for AKI after onset of ARDS. In 2009 influenza A (H1N1) viral pneumonia, the incidence of AKI reached 51% [19]. Another multicenter study showed that AKI occurred in 31.3% of

Table 3. Impact of AKI and risk factors of mortality

Variable	Survivor (n=44)	Non-survivor (n=65)	Multivariate analysis, OR (95% CI)	P-value
AKI	7 (16)	41 (63)	6.8 (1.49–105)	<0.001
KDIGO 1	3 (43)	8 (19.5)		0.322
KDIGO 2	4 (57)	5 (12)		0.017
KDIGO 3	0	28 (68.5)		0.001
Age (yr)	60.5 (56–70)	66 (58–72)	NS	0.048
Obesity	19 (43)	13 (20)	NS	0.007
SOFA score	3 (2–4)	6 (4–11)	NS	0.035
Minimal P/F ratio	93 (65–166)	59 (45–74)	20 (1.73–236)	<0.001
Sepsis	4 (9)	45 (69)	NS	<0.001
Vasopressor	4 (9)	56 (86)	15.29 (1.23–189)	<0.001
MV	5 (11.3)	43 (66)	NS	<0.001

Values are presented as number (%) or median (interquartile range) unless otherwise indicated.
AKI: acute kidney injury; OR: odds ratio; CI: confidence interval; KDIGO: Kidney Disease: Improving Global Outcomes; NS: not significant; SOFA: Sequential Organ Failure Assessment; P/F ratio: the ratio of the arterial partial pressure of oxygen and the inspiratory concentration of oxygen; MV: mechanical ventilation.

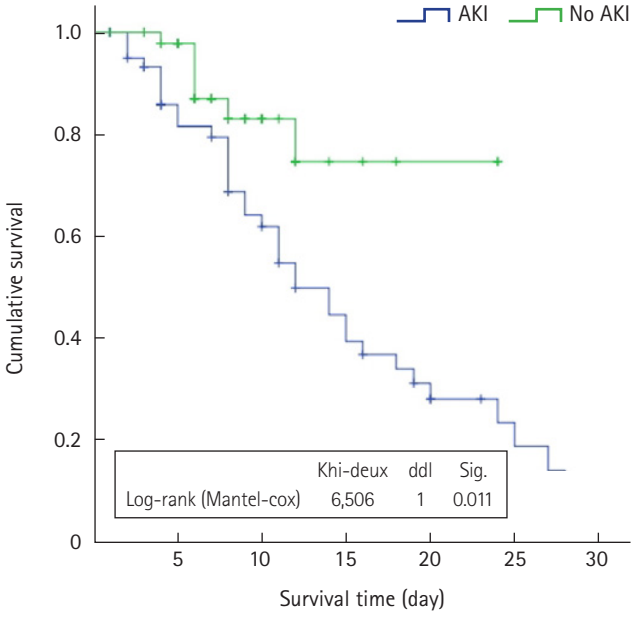

Figure 1. Survival analysis according to presence of acute kidney injury (AKI). ddl: degre de liberte; Sig: significance.

patients and was more common in patients with ARDS (44.3% vs. 27.4%, P<0.001) [20].

In patients with severe COVID-19, the progression to ARDS is almost constant, which partly can explain our elevated number of affected patients. All our patients were deeply hypoxic and required a high flow of oxygen either noninvasively (NIV or/and HFNC in 56%) or invasively (MV in 44%). This partly allows arguing this considerable proportion of AKI. In a Chinese series, the incidence was very close to ours at 43.8% [10]. In our distribution, AKI severity was similar to that in the Chinese study (for stage 3: 58% and 69.6%, respectively) [10]. The high proportion of stage 3 is explained by the serious profile of the patients studied. The median onset of AKI from hospitalization ranges from 7 [11] to 15 days [17], but our delay was shorter at 4 days [1-9]. Before the era of COVID, we conducted a correlation study and we found that the most significant correlation was detected at 48 hours from hypoxemia. This is supported by the present results in the era of COVID-19. Herein, major hypoxemia (judged by a threshold P/F ratio <70) was not an independent factor of AKI (OR, 2.54; P=0.15). Factors other than hypoxemia highly negatively affect the kidney during SARS-CoV-2 invasion.

Analytical Results

We showed that a high level of D-dimers increased the risk of AKI by 13 times. This is an original result and has not been reported previously. What is known is that the significant inflammatory response to the virus causes damage to organs including the kidney. However, neither elevated CRP nor elevated fibrinogens were factors of renal injury (Table 2). D-dimers appear to be the most highly associated factor. Unfortunately, renal histological data were not available in our series to support this finding.

This strong relation suggests the important role of microthrombi in the genesis of AKI. Thrombo-embolic complications during COVID-19 infection have become common, but their extensive involvement in the pathogenesis of AKI is unclear. Based on current evidence, the injured sites and the cor-

responding mechanisms in COVID-19-induced AKI are acute tubular necrosis (due to tubular lumen dilatation with cellular debris and changes in the brush border membranes of proximal tubules), acute interstitial nephritis (due to mononuclear cell infiltration within the interstitium), podocytopathy (due to podocyte foot process effacement, collapsing glomerulus pseudo crescent formation), and thrombotic microangiopathy (due to microthrombi within the glomeruli) [21]. Our results emphasize the significance of the 4th mechanism. A kidney biopsy revealed severe acute thrombotic microangiopathy with cortical necrosis [22]. This disorder cannot be included in the disseminated intravascular coagulation (DIC) entity. In our series, for example, two key diagnostic items of DIC were missing: fibrinogen was rather high (as often is in COVID-19 infection) and platelet count was normal. Clearly, the potential pathological kidney changes in patients with COVID-19 require further study.

Otherwise, we demonstrated that sepsis was close to being a significant factor of COVID-19-induced AKI (OR, 5.22; P=0.058). Sepsis is a condition predisposing the patient to AKI [10,18,23], and AKI is a possible factor in the definition of sepsis according to the last Sepsis-3 consensus [12]. To remove the cause/effect confusion bias (COVID/AKI or sepsis/AKI), we considered sepsis only when it occurred before AKI. The pathogenic mechanisms of sepsis-induced AKI are different from those seen in other causes of AKI.

A review by Zarbock et al. [24] emphasizes the important role of inadequate responses to sepsis. The adaptive responses of tubular epithelial cells to injurious signals are responsible for renal dysfunction. Simultaneously, renal inflammation and microcirculatory dysfunction further amplify these mechanisms [24]. The cytokine storm and micro thrombotic disturbances triggered by SARS-CoV-2 predispose patients with sepsis to AKI compared to those who have not developed sepsis.

In addition to the indirect effects of the immune-inflammatory response to the virus, the direct effects of the viral infection should be considered. These effects largely reflect the ability of the virus to use the ACE2 receptors to gain entry into endothelial cells [25,26]. Since these receptors are widespread in the kidney, they are considered as a potential target for SARS-CoV-2. In our series, AKI did not occur less frequently in patients receiving test drugs, and multivariate analysis did not reveal any protective effect. However, this study was an indirect and not precise assessment of the effects of the virus on the kidney.

Other factors are presumed to be harmful to the kidney and their presence with severe affection caused by SARS-CoV-2 could contribute to the occurrence of AKI. From these factors, we were interested in old age, metabolic morbidities (diabetes and hypertension), MV, vasopressors, rhabdomyolysis, and nephrotoxic drugs. None of these factors were independently associated with AKI. This negative result can be explained by the small size of the studied sample and deserves to be reexamined in a larger population. Different from our findings, Sang et al. [10] showed that MV increased significantly the risk of AKI (OR, 9.72; 95% CI, 2.93–32.24; P=0.0002). This relationship can be explained by the mechanisms of lung-kidney cross-talk [27,28], regardless of the cause of ARDS. Animal models suggest a causal relationship between MV and AKI via a reduction in renal blood flow due to a drop in cardiac output secondary to the changes in intrathoracic pressure; mainly caused by extrinsic positive end-expiratory pressure (PEEP) [29]. Some parameters used for the lung protective ventilation strategy (such as low tidal volume, limited plateau pressure, and suitable level of PEEP) were shown to be protective for AKI [28].

Outcomes

Both our results and other reports [10,11] agree that the occurrence of AKI during COVID-19 worsened morbidity and mortality. Patients of the KDIGO 3 category died more often (OR, 5.33; 95% CI, 1.15–24.65) in a Chinese study [10], and all the patients of our series in this category died. Given the very small number of survivors among the AKI patients (7/48), we did not perform a multivariate analysis to determine the mortality factors in the AKI group with COVID-19. Cheng et al. [11] revealed that patients with initial kidney abnormalities (elevated serum creatinine, proteinuria, hematuria, and AKI) have a significantly higher in-hospital death rate. Beyond AKI, severe hypoxemia with min P/F ratio <150 was independently related to mortality in the study by Sang et al. [10], which was in accordance with our results.

Despite their statistical significance and even if previous studies show supporting findings (i.e., mortality was associated with AKI, other organ failure, or use of vital assistance such as vasopressors or MV), these findings represent a source of confusion. More reasonably, they are consequences of deterioration rather than predictors of deterioration. As an example, many patients with sepsis eventually die with MOF syndrome, and the MOF usually includes AKI. In addition, the largest deterioration was observed in patients who required vital support from MV or vasopressors. Similarly, these factors are

outcomes rather than factors of excess mortality in the present study.

On the other hand, we showed a result (more survivors in the obese subgroup; 43% vs. 20%, P=0.007) that we believe is inconsistent with the most commonly reported findings. Most probably, this was a coincidence without a real association.

We concluded that the proportion of AKI in critically ill patients with COVID-19 was considerable. High levels of D-dimers and, less significantly, sepsis were the most concerning factors. Once they occurred, the prognosis was significantly worse. Early detection and careful monitoring of renal function and D-dimers can help to reduce the deaths of patients with COVID-19. Our findings should place more emphasis on active anticoagulation and further investigation to detect an eventual acute thrombotic microangiopathy caused by SARS-CoV-2.

CONFLICT OF INTEREST

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

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AUTHOR CONTRIBUTIONS

Conceptualization: AT, SA, AA. Data curation: YM, AM, OB, BJ, CA, FD. Formal analysis: AT, SA, AA, SBL. Methodology: AT, AM, OB, ES, FC. Project administration: AT, YM, AM. Visualization: AT, YM, YT, FD. Writing–original draft: AT, YM, YT, BJ, CA. Writing–review & editing: SA, AA, SBL.

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Atrial fibrillation of new onset during acute illness: prevalence of, and risk factors for, persistence after hospital discharge

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Background: Atrial fibrillation (AF) of new onset during acute illness (AFNOAI) has a variable incidence of 1%–44% in hospitalized patients. This study assesses the risk factors for persistence of AFNOAI in the 5 years after hospital discharge for critically ill patients.

Methods: This was a retrospective cohort study. All patients ≥18 years old admitted to the medical intensive care unit (MICU) of a tertiary care hospital from January 1, 2012, to October 31, 2015, were screened. Those designated with AF for the first time during the hospital admission were included. Risk factors for persistent AFNOAI were assessed using a Cox's proportional hazards model.

Results: Two-hundred and fifty-one (1.8%) of 13,983 unique MICU admissions had AFNOAI. After exclusions, 108 patients remained. Forty-one patients (38%) had persistence of AFNOAI. Age (hazard ratio [HR], 1.05; 95% confidence interval [CI], 1.01–1.08), hyperlipidemia (HR, 2.27; 95% CI, 1.02–5.05) and immunosuppression (HR, 2.29; 95% CI, 1.02–5.16) were associated with AFNOAI persistence. Diastolic dysfunction (HR, 1.46; 95% CI, 0.71–3.00) and mitral regurgitation (HR, 2.00; 95% CI, 0.91–4.37) also showed a trend towards association with AFNOAI persistence.

Conclusions: Our study showed that AFNOAI has a high rate of persistence after discharge and that certain comorbid and cardiac factors may increase the risk of persistence. Anticoagulation should be considered, based on a patient's individual AFNOAI persistence risk.

Key Words: atrial fibrillation; paroxysmal atrial fibrillation; persistent atrial fibrillation

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INTRODUCTION

First-time atrial fibrillation (AF) in otherwise medically ill patients without a history of AF has a variable incidence of 1%–44% in hospitalized patients [1,2]. However, it is unclear whether the arrhythmia is transient in this setting, or rather the harbinger of persistent AF in years to come [1]. Here we will refer to this phenomenon as AF of new onset during acute illness (AFNOAI). Risk factors for the long-term persistence of AFNOAI are unknown. Identification of these factors might help guide decisions around initiation of anticoagulation for higher risk individuals. This study assesses the risk factors for persistence of AFNOAI in the 5 years after hospital discharge for critically ill patients.

MATERIALS AND METHODS

Study Design

This was a retrospective cohort study. All patients ≥18 years old admitted to the medical intensive care unit (MICU) of a tertiary care hospital from January 1, 2012, to October 31, 2015, were screened for inclusion. Those designated with AF for the first time during the hospital admission, using a diagnostic code or electrocardiogram (EKG), were included. Patients with pre-existing AF were excluded. AF was verified by analyzing EKG and/or clinical notes. The study was approved by the local Institutional Review Board of the Cleveland Clinic (IRB No. 20-690); informed consent was waived.

Data Acquisition

Relevant demographic, clinical and echocardiographic variables were compiled manually using the electronic medical record. Comorbidities were counted if present on admission. Persistence of AFNOAI or occurrence of stroke/transient ischemic attack was determined via EKG and/or clinical documentation in the 5 years after hospital discharge. Persistent AFNOAI was coded as present if a patient had an AF diagnosis recorded in any clinical documentation in the 5 years following the hospital admission, or an EKG demonstrating AF during this period.

Variable Definitions

For referral status, a referred patient was one who did not present initially to the main tertiary care hospital or one of its in-state regional branches. Chronic kidney disease included stages I-V kidney disease. Malignancy was defined as any active hematologic malignancy or solid tumor. Immunosuppression was defined as the extended use of steroids, steroid-sparing agents, biologics or history of human immunodeficiency virus (HIV). Ischemic heart disease was defined as a history of angina, acute coronary syndrome, coronary artery disease, coronary artery bypass graft or cardiac stents. Hyperlipidemia included elevated triglyceride and/or cholesterol levels. Tobacco smoking was defined as regular tobacco smoking within 1 year of admission. Alcohol excess was defined as regular excess alcohol ingestion within 1 year of admission.

Echocardiographic variables were extracted from an echocardiogram performed within a year of admission. Mitral stenosis and regurgitation included mild, moderate or severe forms. Other valvular heart disease was a history of 3–4+ stenosis or regurgitation of any of the pulmonic, tricuspid or aortic valves. Left atrial dilatation included mild, moderate or severe dilatation. Diastolic dysfunction included grades I–IV dysfunction.

The admission Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) score was used. Hypotension was defined as blood pressure persistently <90/60 mm Hg at any time during admission. Renal failure was defined as new dialysis dependence. Respiratory failure was defined as the need for non-invasive ventilation or intubation. Neurologic failure was defined as altered mental status compared to baseline. Metabolic abnormality included any electrolyte disturbance. Need for transfusion was defined as the need for red blood cell transfusion. Vasopressor use included use of vasopressors at any point during admission.

Statistical Analysis

Baseline variables were expressed as means and standard deviations (continuous variables), or frequencies and percentages (categorical variables). In the first stage of analysis, characteristics of patients with and without AFNOAI persistence were compared using analysis of variance (continuous variables), or Pearson chi-square and Fisher's exact tests (categorical variables). In the second stage, clinically relevant variables, or those with statistically significant univariable associations (P-value of less than 0.05), were included in a multivariable Cox's proportional hazards model to assess risk factors for persistent AFNOAI. Hazard ratios and 95% confidence intervals were reported. Fully conditional specification was used for multiple imputation of missing data. There was no evidence of multicollinearity using variance inflation factors. SAS 9.4 (SAS Institute, Cary, NC, USA) was used for statistical analysis.

KEY MESSAGES

- Atrial fibrillation of new onset during acute illness (AFNOAI) has a high rate of persistence after hospital discharge and is associated with a high in-hospital and 5-year mortality.
- Age, hyperlipidemia, immunosuppression, mitral regurgitation, and diastolic dysfunction may increase the risk of long-term persistence of AFNOAI.

RESULTS

Two-hundred and fifty-one (1.8%) of 13,983 unique MICU

Table 1. Baseline characteristics of patients with and without persistence of AFNOAI in the 5 years after discharge

Variable	AFNOAI persistence	No AFNOAI persistence	P-value
Patient	41 (38.0)	67 (62.0)	-
Demographics			
Age (yr)	70 (57–83)[a]	62 (50–74)[a]	<0.05[a]
Male	29 (70.7)	45 (67.2)	0.70
Referred patients	14 (34.1)[a]	38 (56.7)[a]	0.02[a]
Race			0.54
White	24 (63.2)	46 (70.8)	
Black	13 (34.2)	16 (24.6)	
Comorbidity			
Diabetes mellitus	18 (43.9)	23 (34.3)	0.32
Liver cirrhosis	4 (9.8)	6 (9.0)	0.89
COPD	8 (19.5)	16 (23.9)	0.60
Malignancy	9 (22.0)	22 (32.8)	0.22
Immunosuppression	12 (29.3)	12 (17.9)	0.17
Hypertension	29 (70.7)	38 (56.7)	0.15
Ischemic heart disease	10 (24.4)	20 (29.9)	0.54
Peripheral vascular disease	5 (12.2)	3 (4.5)	0.25
Prior stroke or TIA	6 (14.6)	8 (11.9)	0.69
Hyperlipidemia	23 (56.1)[a]	14 (20.9)[a]	<0.001[a]
OSA	4 (9.8)	6 (9.0)	0.89
Hypothyroidism	8 (19.5)	9 (13.4)	0.40
Chronic kidney disease	13 (31.7)[a]	9 (13.4)[a]	0.02[a]
Obesity (BMI >30 kg/m^2)	18 (47.4)	31 (47.0)	0.97
Tobacco smoking	8 (20.0)	21 (32.3)	0.17
Alcohol excess	5 (12.8)	3 (4.9)	0.26
Echocardiographic variable			
Mitral stenosis	1 (2.6)	0	0.39
Mitral regurgitation	11 (28.2)	10 (16.4)	0.16
Other valvular disease	5 (12.8)	4 (6.6)	0.29
Left atrial dilatation	19 (51.4)	19 (31.7)	0.05
Diastolic dysfunction	21 (56.8)[a]	20 (33.9)[a]	0.03[a]
EF <40	5 (12.8)	9 (15.0)	0.76
Admission diagnosis			0.87
Sepsis	12 (29.2)	18 (26.9)	
Pulmonary disease	10 (24.4)	21 (31.3)	
Gastrointestinal bleed	4 (9.8)	6 (9.0)	
Renal failure	4 (9.8)	3 (4.5)	
Cardiac arrest	2 (4.9)	4 (6.0)	
Other	9 (22.0)	15 (22.4)	
ICU course			
APACHE score	82 (60–104)	76 (49–103)	0.28
Hypotension	23 (56.1)	30 (44.8)	0.25
Vasopressor use	16 (39.0)	24 (35.8)	0.74
Respiratory failure	24 (58.5)	42 (62.7)	0.67
Renal failure	9 (22.0)	16 (23.9)	0.82
Altered mental status	14 (34.1)	23 (34.3)	0.98
Metabolic abnormalities	24 (58.5)	29 (43.3)	0.12
Need for transfusion	22 (53.7)	25 (37.3)	0.10
Outcome variable			
Occurrence of new stroke/TIA	4 (9.8)	1 (1.5)	0.07
Death in 5 years post-discharge	25 (61.0)	34 (50.7)	0.30

Values are presented as number (%) or mean (interquartile range).
AFNOAI: atrial fibrillation of new onset during acute illness; COPD: chronic obstructive pulmonary disease; TIA: transient ischemic attack; OSA: obstructive sleep apnea; BMI: body mass index; EF: ejection fraction; ICU: intensive care unit; APACHE: Acute Physiologic Assessment and Chronic Health Evaluation.
[a]Statistically significant.

admissions had AFNOAI. One-hundred and twenty-six (50%) were excluded due to in-hospital death and 17 (7%) were excluded due to absence of clinical documentation after discharge. One-hundred and eight patients were included. Median follow-up time was 26.0 months (interquartile range [IQR], 6.1–60.0 months).

Table 1 compares characteristics of patients with and without persistence of AFNOAI in the 5 years after discharge. The mean age overall was 65 years (IQR, 52–78 years); 69% were male. Thirty (28%) were admitted for sepsis, 31 (29%) for pulmonary disease, 10 (9%) for gastrointestinal bleed, 6 (6%) for cardiac arrest, 7 (6%) for renal failure, and 24 (22%) for other causes. Eighty percent had AF with rapid ventricular response.

Forty-one patients (38%) had persistence of AFNOAI, with a median time to first documented recurrent AF episode of 6.6 months (IQR, 1.0–29.5 months) after hospital discharge. Five patients (4.6%) had a stroke, of whom 4 had persistent AFNOAI. Fifty-nine (55%) patients died in the 5 years after discharge; median time to death was 9.6 months (IQR, 1.6–24.6 months).

Table 2 shows the results of the Cox's proportional hazards model, using select predictors. Age, hyperlipidemia and immunosuppression were associated with AFNOAI persistence. Diastolic dysfunction and mitral regurgitation (MR) also showed a trend towards association with AFNOAI persistence. Eight patients had no echocardiogram available within a year of admission and seven had incomplete echocardiogram data. Missing data was imputed.

DISCUSSION

Our study describes risk factors associated with the persistence of AFNOAI after critical illness. We found that age, hyperlipidemia and immunosuppression were linked with AFNOAI persistence in our cohort of patients. Diastolic dysfunction and MR may also predispose to persistence. By contrast, disease-associated variables, such as admission diagnosis and organ failure, bore no influence.

Table 2. Effect sizes for variables in Cox's proportional hazards model of time to first recurrent episode of AF after discharge

Variable	Hazard ratio	95% CI	P-value
Age	1.05[a]	1.01–1.08[a]	0.009[a]
Hypertension	0.57	0.21–1.52	0.261
Hyperlipidemia	2.27[a]	1.02–5.05[a]	0.044[a]
Immunosuppression	2.29[a]	1.02–5.16[a]	0.045[a]
Chronic kidney disease	1.07	0.45–2.55	0.876
Diastolic dysfunction	1.46	0.71–3.00	0.308
Left atrial dilatation	1.22	0.57–2.63	0.612
Mitral regurgitation	2.00	0.91–4.37	0.084

AF: atrial fibrillation; CI: confidence interval.
[a]Statistically significant.

The importance of cardiac factors demonstrated in our study reinforces prior data in patients who had undergone non-cardiac surgery, which showed that hypertension and left atrial enlargement were associated with persistence of new onset AF [3]. The association with age likely mirrors the increasing prevalence of AF in the older population [4]. MR and diastolic dysfunction may increase the likelihood of AFNOAI persistence by creating a more arrhythmogenic atrial substrate [4,5]. However, the relationship with hyperlipidemia is ambiguous—other studies have demonstrated both increased and decreased AF risk with respect to hyperlipidemia [6]. Immunosuppression may increase susceptibility to intercurrent illness, including arrhythmias.

Of the five patients who had a stroke, four had persistence of AFNOAI, implying a causal link therein. Indeed, other studies have demonstrated an increased stroke risk in patients with AFNOAI and up to 47.5% of patients did not receive another AF diagnosis before their stroke, highlighting the importance of initiating anticoagulation in a timely fashion [3,7].

The epidemiology of AFNOAI in our study is consistent with previous data, lending credence to the generalizability of our results. AFNOAI was rare in our study (1.8%), but the AFNOAI persistence rate was high (38%), similar to prior research [1,3,7]. Half of patients with AFNOAI expired in hospital, and over half of hospital survivors died in the 5 years after discharge, again consistent with existing evidence of a high mortality rate in this cohort [7-10].

Our study is the first of its kind to look at a vast array of risk factors for persistence of AFNOAI. A limitation is the small sample size. Additionally, some episodes of AFNOAI may have been missed by our screening algorithm, while others may have been clinically silent—in one study only 16.4% of cases were clinically detected [9]. Due to the lack of timely EKGs in patient charts, it was not possible to determine the cardiac rhythm at the time of discharge for each patient—there is potentially a difference in AFNOAI persistence rates between those with sinus rhythm restored at the time of discharge versus those with AF on discharge. Moreover, since patients did not have continuous cardiac monitoring after discharge, it was impossible to tell precisely if and when they first reverted to AF during the 5-year follow-up period. The true AFNOAI

persistence rate may be even higher, if we consider that only symptomatic AF, and AF recorded on EKG, was counted in our study during the follow-up period. Larger prospective studies with continuous cardiac monitoring on discharge are needed to confirm the risk factors for persistent AFNOAI, and whether anticoagulation confers benefit.

Our study showed that AFNOAI has a high persistence rate after discharge and that certain comorbid and cardiac factors may increase the risk of persistence. Stroke prophylaxis should be considered, based on a patient's individual AFNOAI persistence risk, though ultimately such discussion must be framed in the context of the guarded prognosis in this cohort.

CONFLICT OF INTEREST

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

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Bleeding complications associated with the molecular adsorbent recirculating system: a retrospective study

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Background: The molecular adsorbent recirculating system (MARS) is a hepatic replacement system that supports excretory liver function in patients with liver failure. However, since MARS has been employed in our hospital, bleeding complications have occurred in many patients during or after MARS. The objective of this study was to determine how MARS affects coagulopathy and identify specific factors associated with bleeding complications.

Methods: We retrospectively analyzed data from 17 patients undergoing a total of 41 MARS sessions. Complete blood count, coagulation profiles, and blood chemistry values were compared before and after MARS. To identify pre-MARS factors associated with increased bleeding after MARS, we divided patients into bleeder and non-bleeder groups and compared their pre-MARS laboratory values.

Results: MARS significantly reduced bilirubin and creatinine levels. MARS also increased prothrombin time and reduced platelet and fibrinogen, thus negatively impacting coagulation. Pre-MARS hemoglobin was significantly lower in the bleeder group than in the non-bleeder group (P=0.015). When comparing the upper and lower 33% of MARS sessions based on the hemoglobin reduction rate, hemoglobin reduction was significantly greater in MARS sessions involving patients with low pre-MARS international normalized ratio of prothrombin time (PT-INR) and factor V (P=0.038 and P=0.023, respectively).

Conclusions: MARS could appears to alter coagulation-related factors such as factor V and increase the risk of bleeding complications particularly in patient with low hemoglobin. However, individual differences among patients were large, and various factors, such as low hemoglobin, PT-INR, and factor V levels, appear to be involved.

Key Words: artificial liver; blood coagulation disorders; end stage liver disease; extracorporeal life support; hemorrhage

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INTRODUCTION

The treatment of liver failure encompasses symptomatic supportive care as a medical treatment and liver transplantation (LT) as a surgical treatment. The need for intensive critical care is based on the severity of symptoms, such as hemodynamic instability, encephalopathy,

bleeding, and hepatorenal syndrome [1]. LT should be considered upon progression to decompensated liver failure [2]. However, as liver failure progresses rapidly and exhibits a varying course, it is difficult to make early decisions regarding LT in practice. In addition, finding living donors for LT is difficult, and obtaining appropriate cadaveric donors takes a considerable amount of time.

The molecular adsorbent recirculating system (MARS) is a hepatic replacement system that supports excretory liver function in patients with liver failure. It is mainly used as a bridge therapy for patients waiting for LT [3,4]. MARS appears to improve bilirubinemia, hepatic encephalopathy, renal function, and systemic hemodynamics [5]. Although it may be a good option for patients with end-stage liver failure [6], many clinicians are reluctant to apply MARS due to its high price, various side effects, and lack of evidence that it reduces mortality and improves long-term survival rate [7-9]. Adverse effects of MARS include infection, hypotension, severe coagulopathy, bleeding, respiratory failure, cardiac failure, acute pancreatitis, severe thrombocytopenia, and seizure. Of these, bleeding complications are closely linked to mortality among liver failure patients [10], and even if donors are obtained, severe coagulopathy, such as disseminated intravascular coagulation (DIC) can impose a major constraint on LT surgery.

Since MARS has been employed in our hospital, bleeding complications have occurred in many patients during or after MARS, even though coagulation-preventing agents, such as heparin or nafamostat, are not administered. One patient died of bleeding complications, and many others could not proceed with additional MARS sessions. However, other patients showed no bleeding-related complications. Therefore, we sought to determine which patients are more likely to experience bleeding complications and any predictive factors. The purpose of this study was to investigate the association between MARS and bleeding complications, and to identify pre-MARS factors associated with bleeding complications.

KEY MESSAGES

- Molecular adsorbent recirculating system (MARS) is a liver support system that can be useful, but bleeding complication needs to be considered.
- MARS was found to cause significant coagulopathy, resulting in increased bleeding complication.
- Low hemoglobin, low factor V, and prolonged international normalized ratio of prothrombin time in the blood test performed before MARS may have a high likelihood of bleeding complication.

MATERIALS AND METHODS

The Institutional Review Board of Jeonbuk National University Hospital approved this study (IRB No. CUH 2020-03-064). As the study is a retrospective observational one, the need for patient consent was waived.

Data Collection

Data from all patients receiving MARS in the intensive care unit (ICU) between December 2016 and February 2020 were analyzed retrospectively, which included 17 patients undergoing a total of 41 MARS sessions. Laboratory data, hospitalization records, progress records, ICU record sheets, nursing records, transfusion records, and medication history were reviewed. The following data were collected: patients' demographics; predisposing factors; pre-existing liver disease or bleeding; computed tomography abdomen and biopsy findings; Child-Turcotte-Pugh score, Simplified Acute Physiology Score (SAPS) III, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and model for end-stage liver disease (MELD) score; use of continuous renal replacement therapy (CRRT); need for mechanical ventilation and/or vasopressor support during MARS; timing and duration of MARS sessions; transfused blood units; pre-, on-, and post-MARS complete blood cell count, blood chemistry test, blood coagulation test, and coagulation factors; occurrence of LT; current patient status. Most pre- and post-MARS laboratory values were collected shortly before and after MARS, respectively. However, in cases of packed red blood cell (RBC) transfusion during MARS, some post-MARS laboratory values were replaced by on-MARS laboratory values to exclude the effect of transfusion. Coagulation factor values were obtained pre-MARS, 2 hours after the start of MARS, and post-MARS.

MARS Protocol

The main reason of MARS application in our cases are treatment of liver failure to enable native liver recovery, or as a bridge to LT. MARS treatment start in patients who has suitable liver transplant recipient with rapid deterioration of hepatic metabolic function, bilirubin ≥30 mg/dl and type 1 hepatorenal syndrome combined hepatic encephalopathy despite usual medical therapy and with or without acute or chronic liver

disease. However, patients with active bleeding, a tendency to severe bleeding such as DIC and severe thrombocytopenia, or uncontrolled sepsis were excluded [6,11,12]. In addition, due to its very high cost, a comprehensive judgment was made considering factors such as the patient's age, possibility of transplantation, and the opinions of the patient or guardians. Eight hours, at least more than 6 hours, of MARS sessions were repeated based on the daily assessment of the intensivist and medical and surgical hepatology specialists until the patient's clinical condition improved.

The Baxter Gambro Mars kit was used, and heparin priming was performed. A Becton Dickinson arterial cannula was inserted into the brachial or radial artery, and an Arrow's You-Bend double-lumen hemodialysis (HD) catheter (12 Fr) for MARS and Arrow's multi-lumen central venous catheter (7 French, 3-lumen) were inserted into the right jugular, subclavian or femoral vein. HD catheter insertion was performed by radiologic intervention specialists under ultrasound and fluoroscopy to minimize the risk of bleeding as well as possible risks. No agent for preventing coagulation, such as heparin or nafamostat, was administered. Packed RBC, platelet concentrate (PC), fresh frozen plasma (FFP), fibrinogen, cryoprecipitate were transfused for suitable hemodynamics and preventing spontaneous bleeding. According to our medical ICU transfusion protocol, regardless of bleeding, blood products transfusions were performed with the target of hemoglobin ≥7–8 g/dl, platelet ≥ 30 $\times 10^3$/mm^3–50 $\times 10^3$/mm^3, prothrombin time and international normalized ratio (PT-INR) ≤2, and fibrinogen ≥150 mg/dl.

Data Analysis and Statistics Analysis

We first sought to determine the effect of MARS by comparing laboratory values before and after MARS. To identify pre-MARS factors associated with increased bleeding after MARS, we also divided patients into bleeder and non-bleeder groups, according to whether there was visually confirmed or strong suspicion of bleeding after MARS and compared their pre-MARS laboratory values. The bleeder group included patients with suddenly increased catheter insertion site hematoma or ecchymosis, hemoglobin reduction by ≥2 g/dl, need for RBC transfusion with two or more packs, or a marked increase in bleeding after MARS. The non-bleeder group consisted of patients not included in the bleeder group (i.e., patients without catheter insertion site hematoma or ecchymosis, hemoglobin reduction <2 g/dl after MARS, need for RBC transfusion with one or fewer packs, and no marked increase in any bleeding after MARS). We also compared the upper and lower 33% of MARS sessions based on the amount of hemoglobin reduction after MARS, which were designated as bleeding and non-bleeding sessions, respectively. Based on the results, potential factors associated with hemoglobin change rate were analyzed by multiple linear regression analysis.

Patient demographics and baseline values were compared using independent t-tests or chi-square test, as appropriate. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to determine whether data were normally distributed, after which groups were compared using independent t-tests or Mann-Whitney nonparametric tests. Changes over time in factors were tested using repeated measures analysis of variance. All statistical analysis was performed using IBM SPSS statistics ver. 26 (IBM Corp., Armonk, NY, USA).

RESULTS

We examined data from 17 patients undergoing a total of 41 MARS sessions (Tables 1 and 2). The average age of patients was 50 years. Twelve were men, and five were women. Five patients had acute liver failure (ALF; 2 hepatitis A virus, 1 alcoholic, 1 pregnancy-induced, 1 toxic hepatitis), and 12 patients had acute-on-chronic liver failure (AoCLF; 9 alcoholic, 3 hepatitis B virus-related liver cirrhosis). MARS was administered one to six times per patient. At the time of MARS application, 13 of 17 patients were receiving either CRRT or HD, and one started CRRT after MARS was terminated. Ten of the 17 patients died, seven were on an outpatient follow-up. Seven patients underwent LT, one of them died 3 days after surgery and the other died 5 months after surgery. Ten patients did not received LT and two of them recovered spontaneously. Thus, two out of five patients with ALF died, two had native liver recovery, and one survived after LT. On the other hand, eight out of 12 patients with AoCLF died and four survived after LT. Forty MARS sessions were uninterrupted, but one MARS session was stopped after 1 hour due to malfunction of the blood leak detector. The average duration of MARS sessions was 8 hours and 18 minutes.

Eight of the 15 patients presented clinical bleeding complications during or after MARS and were classified into the bleeder group. Seven of these eight patients had catheter bleeding, and three had worsening ecchymosis. In two patient, hemoglobin decreased by <2 g/dl, and in two patients, more than two packs of RBCs were transfused. One patient exhibited subdural hematoma 3 days after MARS and eventually died.

Table 1. Patient's data

No.	Gender/ age (yr)	Predisposing factor	Reason for MARS	No. of MARS	New or increased bleeding sites at the time of MARS	LT	Final outcome
1	M/42	HAV	ALF complicated by HEP and renal dysfunction	3	No	Yes	Expire after 3 days of LT
2	M/47	Herb	ALF complicated by HEP and renal dysfunction	3	No	Yes	Outpatient FU
3	M/62	Alcohol	AoCLF complicated by progressive jaundice and renal dysfunction	3	Catheter insertion site hematoma	No	Expire
4	M/64	Alcohol	AoCLF complicated by progressive jaundice and renal dysfunction	2	No	No	Expire
5	F/28	Pregnancy	ALF complicated by renal dysfunction	1	Vaginal bleeding, catheter insertion site hematoma	No	Outpatient FU
6	M/42	Alcohol, GI bleeding	AoCLF complicated by HEP and renal dysfunction	1	GI bleeding, catheter insertion site hematoma	No	Expire
7	F/51	HBV	AoCLF complicated by progressive jaundice and renal dysfunction	2	Catheter insertion site hematoma	Yes	Outpatient FU, HD
8	M/62	Drug, HBV	AoCLF complicated by progressive jaundice and renal dysfunction	2	No	Yes	Outpatient FU, HD
9	F/35	HAV	ALF complicated by HEP	2	No	No	Outpatient FU
10	F/62	Alcohol	AoCLF complicated by progressive jaundice	2	Brain subdural hemorrhage	No	Expire
11	M/48	Alcohol	AoCLF complicated by progressive jaundice	1	Oral bleeding, catheter insertion site hematoma	Yes	Outpatient FU
12	M/59	HBV	AoCLF complicated by progressive jaundice and renal dysfunction	6	No	Yes	Outpatient FU, HD
13	M/66	Alcohol	AoCLF complicated by progressive jaundice	2	Catheter insertion site hematoma	No	Expire
14	F/26	Alcohol	AoCLF complicated by progressive jaundice	3	No	Yes	Expire after 5 months of LT
15	M/35	Alcohol, GI bleeding	AoCLF complicated by HEP, progressive jaundice, and renal dysfunction	3	No	No	Expire
16	M/42	HBV	AoCLF complicated by HEP, progressive jaundice	2	No	No	Expire
17	M/49	Alcohol, herb	ALF complicated by HEP, progressive jaundice	3	Catheter insertion site hematoma	No	Expire

MARS: molecular adsorbent recirculating system; LT: liver transplantation; HAV: hepatitis A virus; ALF: acute liver failure; HEP: hepatic encephalopathy; FU: follow-up; AoCLF: acute-on-chronic liver failure; GI: gastro-intestinal; HBV: hepatitis B virus; HD: hemodialysis.

In addition, various bleeding events including oral bleeding, bloody sputum, hematuria, melena, or vaginal bleeding occurred or worsened in one or more patients. In patients in the bleeder group, hemoglobin decreased by 1.21 g/dl after MARS, and they received a daily average of 2.18 packs of RBCs, 7.20 packs of PC, 3.82 packs of FFP, and 5.02 packs of cryoprecipitate during the period receiving MARS (from the beginning of the initial MARS to the day following the end of the last MARS). The remaining nine out of 15 patients were classified into the non-bleeder group. Six patients exhibited little bleeding, and three had ecchymosis and catheter bleeding, but did not show much change after MARS. Hemoglobin before MARS decreased by 0.40 g/dl after MARS in the non-bleeder group. During the same period, patients in the non-bleeder group received a daily average of 0.54 packs of RBCs, 2.73 packs of PC, 2.77 packs of FFP, and 2.95 packs of cryoprecipitate.

The amount of change in laboratory values before and after MARS was compared across all patients (Table 3). We found significant changes before and after MARS in hemoglobin, platelet, total bilirubin, direct bilirubin, creatinine, PT-INR, activated partial thromboplastin time (aPTT), fibrinogen, fibrinogen degradation product (FDP), and D-dimer. Total bilirubin and direct bilirubin decreased from 33.0 and 19.5 mg/dl to 28.8 and 16.1 mg/dl though MARS (P<0.001 and P<0.001, respectively). Creatinine decreased by 0.4 mg/dl from 1.8 mg/dl to 1.4 mg/dl (P<0.001). Changes in coagulation profiles after MARS were indicative of a negative coagulation effect. That is, PT-INR, aPTT, FDP, and D-dimer significantly increased, and platelet and fibrinogen significantly decreased after MARS. PT-INR and aPTT was 2.4 INR and 48.1 seconds before MARS but increased to 4.6 INR and 77.6 seconds after MARS (P=0.022 and P=0.017, respectively). Fibrinogen de-

Table 2. Patient's baseline values before molecular adsorbent recirculating system

Variable	All patients (n=17)	Bleeder (n=8)	Non-bleeder (n=9)	P-value
Male	12 (70.6)	5 (62.5)	7 (77.8)	0.490
Age (yr)	50.0±13.9	51.3±13.5	46.3±14.2	0.673
Underlying liver cirrhosis	12 (70.6)	6 (75.0)	6 (66.7)	0.707
End stage renal disease	0	0	0	1.000
Disease severity				
CTP score	10.9±1.4	10.8±1.4	11.0±1.6	0.888
MELD score	38.5±6.8	39.9±5.7	37.3±7.9	0.481
SAPS III score	62.3±10.0	63.0±10.7	61.7±10.0	1.000
APACHE II score	16.1±6.9	17.5±7.3	14.9±6.6	0.481
Support modality				
CRRT	13 (76.5)	7 (87.5)	6 (66.7)	0.312
Mechanical ventilation	4 (23.5)	3 (37.5)	1 (11.1)	0.079
Vasopressor	6 (35.3)	4 (50.0)	2 (22.2)	0.079
Laboratory parameter				
Hemoglobin (g/dl)	9.7±2.1	9.1±2.4	10.3±1.6	0.015
Platelet ($\times 10^3/mm^3$)	77.4±46.2	84.6±55.6	70.9±38.2	0.606
AST (IU/L)	673±1,360	352±635	958±1,776	0.200
ALT (IU/L)	600±1,045	359±678	814±1,293	0.200
Total bilirubin (mg/dl)	30.9±12.7	30.2±11.7	31.5±14.3	0.743
Direct bilirubin (mg/dl)	18.8±8.9	15.4±5.9	21.7±10.4	0.139
Albumin (g/dl)	3.2±0.3	3.3±0.3	3.2±0.3	0.236
Creatinine (mg/dl)	1.9±1.1	1.7±0.4	2.1±1.5	0.673
Ammonia (μmol/L)	89.7±46.9	91.5±61.8	88.2±32.6	0.541
LD (IU/l)	1,491±1,692	1,316±1,348	1,647±2,019	0.673
PT-INR	2.5±0.8	2.7±1.0	2.3±0.4	0.606
aPTT (sec)	48.0±10.9	46.1±7.4	49.8±13.6	0.963
Fibrinogen (mg/dl)	151.7±51.6	133.9±56.4	169.5±42.4	0.161
FDP (mg/ml)	62.0±58.4	69.4±55.7	53.5±64.6	0.613
Anti-thrombin III (%)	28.0±14.5	25.6±13.7	30.4±15.9	0.645
D-dimer (mg/L FEU)	15.3±15.7	14.9±13.2	15.9±19.3	0.955
Factor II (%)	31.5±7.9	31.3±6.9	31.7±9.1	1.000
Factor V (%)	27.4±16.9	16.0±7.7	35.0±17.4	0.067
Factor VII (%)	19.1±7.8	17.5±9.8	20.2±6.9	0.914
Factor X (%)	39.8±15.4	35.5±11.1	42.7±18.2	1.000
Procalcitonin (ng/ml)	2.0±1.9	1.3±0.8	2.6±2.4	0.321
Lactate (mmol/L)	3.2±2.0	3.3±2.5	3.0±1.6	0.673

Values are presented as number (%) or mean±standard deviation.
CTP: Child-Turcotte-Pugh; MELD: model for end-stage liver disease; SAPS: Simplified Acute Physiology Score; APACHE: Acute Physiology and Chronic Health Evaluation; CRRT: continuous renal replacement therapy; AST: aspartate transaminase; ALT: alanine aminotransferase; LD: lactate dehydrogenase; PT-INR: international normalized ratio of prothrombin time; aPTT: activated partial thromboplastin time; FDP: fibrinogen degradation product; FEU: fibrinogen equivalent unit.

creased from 155.4 mg/dl to 98.1 mg/dl (P=0.021), and platelet also decreased from 78.8 $\times 10^3/mm^3$ to 63.5 $\times 10^3/mm^3$ (P=0.002). These resulted in a decrease in hemoglobin from 9.4 g/dl to 8.8 g/dl (P<0.001). In addition, Figure 1 shows changes in coagulation factors measured before MARS, 2 hours after the start of MARS, and after MARS finish. There were no significant differences changes before and after MARS in other chemistry profiles, or inflammatory markers.

Table 3. Changes in values before and after MARS (n=41)

Variable	Before MARS	After MARS	P-value
Complete blood count			
Hemoglobin (g/dl)	9.4±1.7	8.8±1.8	<0.001
Platelet (×10^3/mm^3)	78.8±35.2	63.5±35.1	0.002
Chemistry profile			
AST (IU/L)	444±924	389±654	0.586
ALT (IU/L)	470±836	422±713	0.126
Total bilirubin (mg/dl)	33.0±11.6	28.8±9.0	<0.001
Direct bilirubin (mg/dl)	19.5±7.7	16.1±5.7	<0.001
Albumin (g/dl)	3.3±0.4	3.4±0.5	0.119
Creatinine (mg/dl)	1.8±1.0	1.4±0.7	<0.001
Ammonia (μmol/L)	92.2±52.5	87.6±45.7	0.133
LD (IU/L)	1,320±1,157	1,266±787	0.728
Coagulation profile			
PT-INR	2.4±0.8	4.6±6.0	0.022
aPTT (sec)	48.1±14.2	77.6±76.4	0.017
Fibrinogen (mg/dl)	155.4±28.1	98.1±64.1	<0.001
FDP (mg/ml)	107±107	189±121	<0.001
Anti-thrombin III (%)	30.6±13.6	34.4±13.2	0.141
D-dimer (mg/L FEU)	34.2±44.8	66.6±53.6	<0.001
Coagulation factor			
Factor II (%)	34.7±9.3	32.0±10.6	0.014
Factor V (%)	30.1±17.6	21.9±17.1	<0.001
Factor VII (%)	21.2±9.8	19.7±9.3	0.008
Factor X (%)	44.4±16.0	41.4±16.3	0.003

Values are presented as mean±standard deviation.
MARS: molecular adsorbent recirculating system; AST: aspartate transaminase; ALT: alanine aminotransferase; LD: lactate dehydrogenase; PT-INR: international normalized ratio of prothrombin time; aPTT: activated partial thromboplastin time; FDP: fibrinogen degradation product; FEU: fibrinogen equivalent unit.

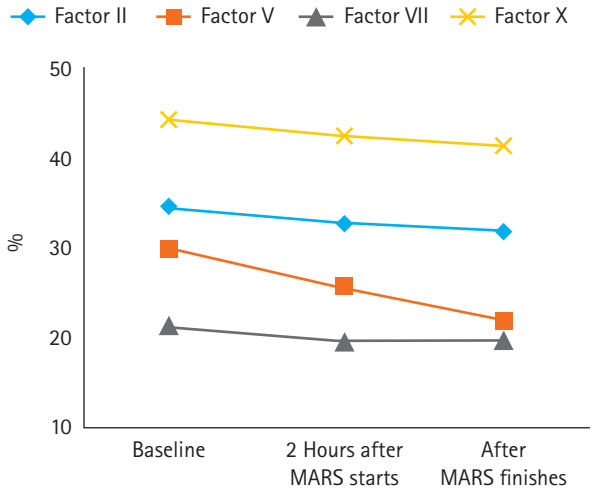

Figure 1. Sequential measurements of coagulation factors (n=27). All factors (factor II, V, VII, and X) decreased significantly over time (P=0.012, P<0.001, P=0.001, and P=0.002, respectively). Note that factor V sharply decreased from 30.1% before molecular adsorbent recirculating system (MARS) to 25.8% and 21.9%, respectively, 2 hours after MARS started and after MARS finished.

Table 2 presents pre-MARS values for patients in the bleeder and non-bleeder groups. Pre-MARS hemoglobin was significantly lower in the bleeder group (9.1 g/dl) than in the non-bleeder group (10.3 g/dl; P=0.015). Apart from hemoglobin, however, there were no significant differences between patient groups.

Table 4 shows a comparison of the upper and lower 33% of MARS sessions based on hemoglobin reduction rate. After MARS, hemoglobin decreased by 1.49 g/dl on average in the upper 33% of sessions (i.e., bleeding sessions) and increased by 0.15 g/dl in the lower 33% of sessions (i.e., non-bleeding sessions). Pre-MARS PT-INR was significantly higher for bleeding sessions (2.7 INR) than for non-bleeding sessions (2.0 INR; P=0.038). Also, pre-MARS factor V was significantly lower for bleeding sessions (24.8%) than for non-bleeding sessions (45.6%; P=0.023). Other values did not significantly differ between groups.

Multiple linear regression analysis was performed to verify the effect of pre-MARS factors potentially associated with hemoglobin change rate through MARS (Table 5). The results of verifying the significance of the regression coefficient show that pre-MARS hemoglobin, PT-INR, and factor V have a significant effect on the hemoglobin change rate, whereas pre-MARS platelet, total bilirubin, albumin, fibrinogen, and anti-thrombin do not. That is, the B value of the pre-MARS PT-INR was –5.227 (P=0.036), and as the pre-MARS PT-INR increased by 1 INR, the post-MARS hemoglobin decreased by 5.227%. The decrease of 1 g/dl hemoglobin and 1% factor V in pre-MARS can also be predicted to decrease post-MARS hemoglobin by 2.443% and 0.281%, respectively.

DISCUSSION

Our results show that MARS acts as a liver support system by reducing total bilirubin, direct bilirubin, and creatinine. However, MARS may increase the risk of bleeding by increasing PT and aPTT and reducing platelet and fibrinogen. As a result, hemoglobin levels decreased by 0.6 g/dl on average after MARS compared to before MARS. When comparing MARS sessions between two groups according to bleeding and hemoglobin

Table 4. Pre-MARS values for bleeding and non-bleeding sessions based on rate of hemoglobin decrease during MARS

Variable	Bleeding sessions (n=14)	Non-bleeding sessions (n=13)	P-value
Support modality			
CRRT	11 (78.6)	9 (69.2)	0.685
Mechanical ventilation	4 (28.6)	1 (7.7)	0.375
Vasopressor	4 (28.6)	1 (7.7)	0.375
Complete blood count			
Hemoglobin (g/dl)	9.4±2.2	10.1±1.5	0.054
Platelet (×10^3/mm^3)	87.2±41.3	89.7±30.4	0.616
Laboratory parameter			
AST (IU/L)	347±499	857±1506	0.519
ALT (IU/L)	350±599	986±1213	0.239
Total bilirubin (mg/dl)	34.1±11.1	25.1±13.3	0.066
Direct bilirubin (mg/dl)	19.6±7.7	16.7±9.1	0.379
Albumin (g/dl)	3.3±0.4	3.4±0.4	0.820
Creatinine (mg/dl)	1.8±0.9	1.5±0.8	0.759
Ammonia (μmol/L)	95.5±72.0	96.0±40.9	0.350
LD (IU/L)	1,265±1,088	1,534±1,690	0.943
Coagulation profile			
PT-INR	2.7±1.1	2.0±0.3	0.038
aPTT (sec)	46.4±5.8	45.5±13.5	0.141
Fibrinogen (mg/dl)	163±84	159±43	0.859
FDP (mg/ml)	106.9±106.8	98.4±98.7	0.810
Anti-thrombin III (%)	26.6±12.4	26.4±7.7	0.955
D-dimer (mg/L FEU)	32.1±45.6	32.3±39.5	0.689
Coagulation factor			
Factor II (%)	33.5±8.8	39.6±10.8	0.270
Factor V (%)	24.8±16.8	45.6±21.2	0.023
Factor VII (%)	19.3±9.2	25.0±8.3	0.222
Factor X (%)	41.5±15.2	52.3±18.9	0.212

Values are presented as number (%) or mean±standard deviation.
MARS: molecular adsorbent recirculating system; CRRT: continuous renal replacement therapy; AST: aspartate transaminase; ALT: alanine aminotransferase; LD: lactate dehydrogenase; PT-INR: international normalized ratio of prothrombin time; aPTT: activated partial thromboplastin time; FDP: fibrinogen degradation product; FEU: fibrinogen equivalent unit.

Table 5. Multiple linear regression analysis of pre-MARS factors potentially associated with hemoglobin change rate (%)

Independent variable	Unstandardized coefficient		Standardized coefficient	P
	B	SE	β	
Hemoglobin (g/dl)	2.443	0.994	0.460	0.020
Platelet (×10^3/mm^3)	−0.072	0.046	−0.281	0.132
Total bilirubin (mg/dl)	0.153	0.157	0.198	0.338
Albumin (g/dl)	6.657	3.948	0.280	0.101
PT-INR	−5.227	2.389	−0.462	0.036
Fibrinogen (mg/dl)	−0.030	0.027	−0.185	0.284
Anti-thrombin III (%)	−0.132	0.102	−0.199	0.206
Factor V (%)	0.281	0.125	0.434	0.032

F=2.582 (P=0.027), adjR^2=0.240, Durbin-Watson=2.154.
MARS: molecular adsorbent recirculating system; SE: standard error; PT-INR: international normalized ratio of prothrombin time.

change, parameters that differed significantly between two groups were pre-MARS hemoglobin, PT-INR, and factor V, and multiple linear regression analysis also indicates that these three factors are independently related to the hemoglobin change rate. This suggests that low hemoglobin, low factor V, and prolonged PT-INR in the blood test performed before MARS may have a high likelihood of bleeding complication.

Lower pre-MARS hemoglobin in the bleeding group suggests that bleeding, including micro-bleeding, may have been present prior to MARS, unless the patient had underlying anemia, chronic kidney disease, or hematological disease. There were no differences in pre-MARS parameters between bleeder and non-bleeder groups except for hemoglobin, and no patient had underlying chronic kidney disease. Thus, our results suggest that MARS increases bleeding risk when a tendency toward bleeding already exists. Pre-MARS platelet count, PT, and aPTT did not significantly differ between groups. As individual differences in bleeding tendency exist, laboratory values may not fully reflect a patient's bleeding tendency.

The liver is the site where fibrinogen and factors II, V, VII, IX, X, XI, and XII are synthesized. In patients with hepatic insufficiency, levels of these factors are low due to protein dysfunction and poor synthetic function. Defects in γ-carboxy-glutamic acid residues introduced by vitamin K-dependent carboxylase result in deterioration of the functions of factor II, VII, IX, and X and proteins C and S. By contrast, although factor V is mainly synthesized in the liver, it is a vitamin K- independent coagulation factor [13]. This may be the basis for the fact that the plasma half-life of factor V is relatively short, about 12–24 hours, and a decrease in factor V is the most sensitive indicator of liver failure [14,15]. Many studies also suggest that factor V levels are related to survival and can serve as a prognostic indicator [16-18]. Interestingly, the gene for factor V related to the family of multi-copper oxidases, and is homologous to coagulation factor VIII. Activated factor V (factor Va) is a major cofactor of the prothrombinase complex. The activated factor X enzyme requires calcium and factor Va to convert prothrombin to thrombin on the cell surface membrane. Factor Va is degraded by activated protein C,

one of the principal physiological inhibitors of coagulation. In the presence of thrombomodulin, thrombin acts to decrease clotting by activating protein C; therefore, the concentration and action of protein C are important determinants in the negative feedback loop through which thrombin limits its own activation. Because this study was a simple retrospective observational study, we did not predict the association of factor V related-MARS complication and not check the protein C and von Willebrand factor. There is a limitation in studying additional associations such as protein C and other factors related to coagulation.

Many studies suggest that MARS reduces bilirubin and creatinine and improves hepatic encephalopathy [3]. However, its side effects such as bleeding complication and survival rate are somewhat controversial. A meta-analysis published in 2012 [5] reported that MARS reduced total bilirubin and clinical symptoms of hepatic encephalopathy, but had no effect on survival. In a meta-analysis published in 2019 [7], there was no difference in the survival of patients receiving standard medical support or MARS, but patients receiving high-intensity therapy with five or more MARS sessions showed better survival than those receiving low-intensity therapy with four or fewer sessions. They also found that the incidence of bleeding complications in the MARS group was 24.1% compared to 10.2% of patients receiving standard medical care (P=0.007). A meta-analysis published in 2020 [19] reports that MARS reduces mortality (relative risk [RR], 0.84; moderate certainty) among patients with ALF or AoCLF and is associated with bleeding-related side effects, such as hypotension (RR, 1.46; low certainty), bleeding (RR, 1.21; moderate certainty), and thrombocytopenia (RR, 1.62; very low certainty). Bleeding complications of MARS can induce an unstable hemodynamic state, increase blood transfusion demand, and impede the procedure [20,21]. Bleeding complications can also promote DIC in patients with liver failure, making medical staff hesitant to proceed with LT [10].

Many recent studies of MARS mention bleeding-associated side effects, such as thrombocytopenia, coagulopathy, hypofibrinogenemia, and anemia, but few studies focus on these outcomes. Among them, several studies using viscoelastic tests such as thromboelastography (TEG) or rotational thromboelastometry (ROTEM) indicate that MARS induces platelet-mediated coagulopathy, both mechanically and immunologically [22,23]. MARS is an extracorporeal circulation system that potentially activates coagulation by putting blood in contact with artificial materials, resulting in the consumption of coagulation factors and platelets. We found that MARS significantly reduced platelet count by 15.3 $\times 10^3/mm^3$ and also reduced coagulation factors, especially factor V. Moreover, the large-bore venous cannulation (12 Fr) required for MARS may be a factor that causes bleeding in liver failure patients with coagulopathy. In this study, nine out of 17 patients (53%) had a bleeding complication, and eight out of nine patients (89%) had muscle or subcutaneous bleeding or hematoma related to catheter insertion. This differs significantly from the study in patients with ALF who received supportive care without MARS. The study found a 10.6% incidence of bleeding complications, of which 11% were procedure-related [10]. Double-lumen HD catheter (12Fr) and arterial line catheters were inserted in all patients so that bleeding tendency could be evaluated under the similar conditions. Unlike previous studies, we did not use heparin during MARS treatment and controlled the effects of blood transfusions such as packed RBCs, PC, and FFP.

Our study has several limitations. First, the number of patients was somewhat small, and the data collection period was long. Second, Due to its retrospective design, the time that laboratory testing was performed differed slightly across patients. Moreover, there was an inevitable difference in timing because we had to select two time points between which blood transfusion was not performed. Third, we cannot rule out the subjectivity of the researcher, as we grouped patients primarily based on their visible bleeding. The frequency of bleeding complications after MARS in our study was much higher than that in previous studies, even though heparin was not used. To explain this discrepancy, we reviewed the MARS procedure several times and contacted the MARS kit manufacturer to ensure that there were no changes in the kit or its recommended use instructions. Forth, as a retrospective study, viscoelastic tests such as TEG or ROTEM were not performed during the study period. These were not our routine practice.

In conclusion, MARS could appears to alter coagulation-related factors, such as platelet count, PT, aPTT, fibrinogen, and coagulation factors, and increase the tendency toward bleeding complications particularly in patients with low hemoglobin. Therefore, the progression of coagulopathy should be considered when proceeding with MARS. However, the differences observed among patients were large, and various factors, such as pre-MARS hemoglobin, PT-INR and factor V, appear to contribute to these differences. Further research on this subject is warranted given that the ability to predict bleeding complications, before their onset, would be useful to clinicians when making decisions regarding the use of MARS.

CONFLICT OF INTEREST

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

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Association of natural light exposure and delirium according to the presence or absence of windows in the intensive care unit

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Background: Patients in the intensive care unit (ICU) have increased risks of delirium, which is associated with worse outcomes. As pharmacologic treatments for delirium are ineffective, prevention is important. Nonpharmacologic preventive strategies include exposure to natural light and restoring circadian rhythm. We investigated the effect of exposure to natural light through windows on delirium in the ICU.

Methods: This retrospective cohort study assessed all patients admitted to the medical ICU of a university-affiliated hospital between January and June 2020 for eligibility. The ICU included 12 isolation rooms, six with and six without windows. Patients with ICU stays of >48 hours were included and were divided into groups based on their admission to a single room with (window group) or without windows (windowless group). The primary outcome was the cumulative incidence of delirium. The secondary outcomes were the numbers of delirium-and mechanical ventilation-free days, ICU and hospital length of stay, and in-ICU and 28-day mortalities.

Results: Of the 150 included patients (window group: 83 [55.3%]; windowless group: 67 [44.7%]), the cumulative incidence of delirium was significantly lower in the window group than in the windowless group (21.7% vs. 43.3%; relative risk, 1.996; 95% confidence interval [CI], 1.220–3.265). Other secondary outcomes did not differ between groups. Admission to a room with a window was independently associated with a decreased risk of delirium (adjusted odds ratio, 0.318; 95% CI, 0.125–0.805).

Conclusions: Exposure to natural light through windows was associated with a lower incidence of delirium in the ICU.

Key Words: delirium; intensive care unit; light

INTRODUCTION

Delirium is common in intensive care units (ICUs) [1,2] and is characterized by a disruption in cognition and attention with a change in awareness and fluctuating course. Delirium in the ICU is associated with worse outcomes such as prolonged hospital length of stay (LOS) [1,3], a longer duration of mechanical ventilation, and increased risks of reintubation and cognitive impairment in survivors [4], as well as increased mortality and morbidity [5-7].

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Delirium is caused by a variety of factors. The risk factors can be categorized as non-modifiable and potentially modifiable [8]. Major host factors associated with delirium in the ICU are old age [6,9] which is one of the most important risk factors, illness severity, previous dementia, malnutrition, past coma history, and emergency surgery or trauma prior to ICU admission [10]. Iatrogenic and other possibly modifiable factors are mainly responsible for environmental variables including the absence of visible daylight, immobility, isolation, or physical restraints. [8,9]. Benzodiazepines are also an independent contributing factor for the occurrence of delirium among the sedatives during ICU care [9,10].

Whether intensive care environments affect the progression of delirium and its outcomes remains poorly understood. Most ICUs use non-pharmacological methods, including multicomponent ABCDEF bundles (i.e., awakening and breathing coordination, delirium monitoring/management, and early exercise/mobility [ABCDE]), to reduce or prevent delirium [11]. Improvements in bundle adherence were substantially associated with lower mortality rates and more ICU days free of coma or delirium [12-14]. However, there is a paucity of data on the relationship between light exposure and delirium in the ICU. Patients with delirium in the ICU have disturbed sleep-wake cycles and circadian rhythms because due to constant exposure to artificial light [15,16]. This may disturb the natural sleep-wake cycle and make patients more vulnerable to delirium [15,17]. A recent single-center, before-after study showed a reduction in the incidence and duration of delirium in patients admitted to a new ICU room with higher exposure to light through windows compared to the old ICU with lower light intensity [18]. In comparison, a multicenter randomized control trial found that, compared to standard lighting, the application of high-intensity dynamic light did not reduce the overall incidence of delirium [19].

The present study investigated the effect of natural light exposure through windows on the incidence of delirium in critically ill patients admitted to single rooms in the ICU.

KEY MESSAGES

- We investigated the effect of exposure to natural light through windows on delirium in the intensive care unit (ICU).
- This retrospective cohort study, the cumulative incidence of delirium was significantly lower in the window group compared to that in the windowless group (21.7% vs. 43.3%; relative risk, 1.996; 95% confidence interval, 1.220–3.265).
- Exposure to natural light through windows was associated with a lower incidence of delirium in the ICU.

MATERIALS AND METHODS

Statement of Ethics

This study was approved by the Institutional Review Board of Seoul National University Hospital (IRB No. 2012-155-1183). The informed consent from participants was waived or not required due to the retrospective study.

Study Design and Participants

This retrospective, observational study was conducted in the 12-bed medical ICU (MICU) of Seoul National University Hospital between January 1, 2020, and June 30, 2020. Among the 12 isolation rooms, six had windows and six did not. There was no admission policy regarding room allocation, and patients were typically assigned to the "first available room."

Patients with more than 2 days of MICU stay were eligible for study inclusion. The patients were divided into two groups depending on whether they were admitted to a room with (window group) or without windows (windowless group). Patients were excluded if they were transferred from other ICUs, had acute brain injury, or had preexisting conditions known to interfere with delirium assessment (e.g., blindness, deafness, and overt dementia).

Delirium Assessment

The level of sedation and agitation of each patient was monitored using the Richmond agitation sedation scale (RASS) six times per day by trained bedside nurses. Every patient in the MICU was screened for delirium once a day by the attending nurse using Confusion Assessment Method for the ICU (CAM-ICU). Delirium was diagnosed based on the presence of one or more of the following conditions: (1) positive CAM-ICU findings, (2) diagnosis made by physicians from the department of mental health, (3) administration of antipsychotics to treat delirium, and (4) clinical suspicion by the attending physician. The number of days with delirium was counted cumulatively during ICU stay. A day was categorized as "delirium and coma-free" if the patient was alive without delirium and not in a coma from any cause. Patients who died within 14 days of ICU admission were recorded as having 0 days free of delirium and coma. Any day with a positive RASS or a pharmacologic inter-

vention with antipsychotics to treat hyperactive symptoms was considered to be a day of agitation.

ICU Environment

All six windowed rooms face south. The patient's head is placed towards the window side and the details of the ICU room is presented in Supplementary Figures 1 and 2. The window size was 140×220 cm in width and length respectively. Illuminance of ambient and artificial light levels were measured in each ICU rooms at 10:00 AM, 2:00 PM, 6:00 PM for 2 consecutive days at the patient's eye level (reflective measurement) (Supplementary Table 1). The digital light meter used was LUX HiTESTER 3423 manufactured by HIOKI (Koizumi, Ueda, Japan). The shades on the windows were always left open and the artificial lighting was always turned on in both rooms. The brightness was adjusted only when examinations requiring dark lighting such as ultrasound were performed or during the night hours.

Variables and Their Definitions

The covariates in this study included age, sex, body mass index, history of tobacco smoking, alcohol abuse, comorbidities (e.g., hypertension, diabetes mellitus, chronic liver disease, chronic kidney disease, cardiovascular disease, cerebrovascular disease, cognitive disorder, and chronic obstructive pulmonary disease), and history of medication use (e.g., antipsychotics, benzodiazepine, other sedatives, and steroid).

The cause of ICU admission was determined based on the following diagnoses: respiratory failure, renal replacement therapy, cardiogenic failure, postoperative care, sepsis, hypovolemic shock, and other (e.g., close monitoring or physician's concern).

The severity of illness at ICU admission was assessed using the Acute Physiology and Chronic Health Evaluation (APACHE) II score, Simplified Acute Physiology Score (SAPS) II, and Sequential Organ Failure (SOFA) score. The use of opioids (e.g., remifentanil, morphine, and fentanyl) and sedatives (e.g., midazolam, propofol, and dexmedetomidine) during each patient's stay in the MICU was also recorded.

Outcome Variables

The primary outcome was the cumulative incidence of delirium, defined as the presence of delirium during the ICU stay. The secondary outcomes were the number of delirium and coma-free days, the incidence of agitation, number of mechanical ventilation-free days, ICU and hospital LOS, and in-ICU and 28-day mortalities.

Statistical Analysis

Data are presented as average±standard error, median (interquartile range) or numbers (percentage) for continuous and categorical variables, respectively. Student t-tests were used to study independent samples of continuous, normally distributed data, while Mann-Whitney U-tests were used to assess continuous, skewed data. Chi-square tests were used to analyze categorical data. We used multivariate logistic regression analysis to study the association between the two groups and the occurrence of delirium. The following variables were selected as potential confounding factors: age, alcohol abuse, mechanical ventilation, duration of mechanical ventilator apply, self-extubation, use of vasoactive agents, duration of midazolam administration, duration of propofol administration, duration of dexmedetomidine administration and clinically relevant factors associated with delirium in the univariate analysis ($P<0.05$) were entered into a multivariate model (Supplementary Table 2).

Kaplan-Meier survival curves were used to estimate the probability of delirium events and compared using log-rank tests. Cox proportional hazard regression models were constructed to calculate adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) for the association between the factors and the time to first delirium event, adjusted for the confounders mentioned above.

RESULTS

Between January 2020 and June 2020, 208 patients were admitted to the MICU, 150 of whom (windowless group, n=67; window group, n=83) were included after excluding 58 patients. Among the 58 excluded patients, 51 had a MICU LOS of less than 48 hours, and seven patients were transferred from other ICUs (surgical ICU, emergency ICU, cardiac care unit). The baseline characteristics of the included patients are presented in Table 1. The baseline characteristics, including age, sex, and severity scores, were similar between the windowless and the window groups. There were more antipsychotic use (12% vs. 3%, P=0.042) and less alcohol abuse (6% vs. 10.7%, P=0.033) in the window group compared to the windowless group. Most comorbidities were distributed similarly between the two groups, although there were more patients with chronic liver disease in the windowless group compared to the window group (19.4% vs. 8.4%, P=0.049). The most common cause for

Table 1. Baseline patient characteristics

Variable	All (n=150)	Windowless (n=67)	Window (n=83)	P-value
Age (yr)	69 (60–77)	69 (55–77)	69 (60–78)	0.979
Body mass index (kg/m^2)	21.7±0.4	21.6±0.5	21.7±0.5	0.727
Male	87 (58.0)	33 (49.3)	54 (65.1)	0.051
Smoking				0.110
Ever	54 (36.0)	18 (26.9)	36 (43.4)	
Never	79 (52.7)	40 (59.7)	39 (47.0)	
Alcohol abuse	25 (16.7)	16 (10.7)	9 (6.0)	0.033
Underlying disease				
Hypertension	71 (47.3)	28 (41.8)	43 (51.8)	0.222
Diabetes mellitus	66 (44.0)	29 (43.3)	37 (44.6)	0.874
Chronic liver disease	20 (13.3)	13 (19.4)	7 (8.4)	0.049
Chronic kidney disease	46 (30.7)	20 (29.9)	26 (31.3)	0.846
Cardiovascular disease	47 (31.3)	9 (28.4)	28 (33.7)	0.480
Cerebrovascular disease	14 (9.3)	5 (7.5)	9 (10.8)	0.479
Cognitive disorder	4 (2.7)	1 (1.5)	3 (3.6)	0.423
Chronic obstructive pulmonary disease	4 (2.7)	2 (3.0)	2 (2.4)	0.828
Medical history				
Antipsychotics	12 (8.0)	2 (3.0)	10 (12.0)	0.042
Benzodiazepine	15 (10.0)	7 (10.4)	8 (9.6)	0.870
Sedative	13 (8.7)	3 (4.5)	10 (12.0)	0.101
Steroid	44 (29.3)	21 (31.3)	23 (27.7)	0.627
ICU admission diagnosis				
Respiratory failure	96 (64.0)	44 (65.7)	52 (62.7)	0.702
Renal replacement therapy	27 (18.0)	13 (19.4)	14 (16.9)	0.688
Cardiogenic failure	28 (18.7)	13 (19.4)	15 (18.1)	0.835
Postoperative care	2 (1.3)	0	2 (2.4)	0.201
Sepsis	26 (17.3)	10 (14.9)	16 (19.3)	0.484
Hypovolemic shock	2 (1.3)	2 (3.0)	0	0.113
Others[a]	16 (10.7)	7 (10.4)	9 (10.8)	0.938
Mechanical ventilation	121 (80.7)	51 (76.1)	70 (84.3)	0.205
Vasoactive agents	80 (53.3)	42 (28.0)	38 (25.3)	0.039
Norepinephrine	49 (32.7)	22 (32.8)	27 (32.5)	0.968
Epinephrine	16 (10.7)	15 (22.3)	1 (1.2)	<0.001
Dopamine	28 (18.7)	13 (19.4)	15 (18.1)	0.835
Dobutamine	4 (2.7)	1 (1.5)	3 (3.6)	0.423
Vasopressin	28 (18.7)	12 (17.9)	16 (19.3)	0.831
APACHE II score	19.5 (15–27)	19 (15–26)	21 (15–28)	0.476
SOFA score	9 (6–12)	9 (6–11)	9 (6–13)	0.302
SAPS II	45.9±1.7	45.1±2.3	46.6±2.4	0.656

Values are presented as median (interquartile range), mean±standard error, or number (%).
ICU: intensive care unit; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sepsis Organ Failure Assessment; SAPS: Simplified Acute Physiology Score.
[a]Others: closed observation, physician's concern, etc.

ICU admission was respiratory failure, followed by cardiogenic failure. The majority of vasoactive drugs used throughout the ICU stay were comparable between the two groups but the number of patients treated with epinephrine were higher in the windowless group.

Most of the enrolled patients were administered opioids (80%) and sedatives (83.3%) during their stay in the ICU. The most commonly administered opioid was remifentanil followed by fentanyl, while the most commonly administered sedative was dexmedetomidine followed by midazolam. There was no difference in opioid and sedative exposures between the groups (Table 2).

Table 2. Opioid and sedative use during intensive care unit stay

Variable	All (n=150)	Windowless (n=67)	Window (n=83)	P-value
Opioid	120 (80)	50 (74.6)	70 (84.3)	0.139
Remifentanil				
Patient	101 (67.3)	42 (62.7)	59 (71.1)	0.276
Cumulative duration (day)	3 (0–7)	2 (0–7)	3 (0–7)	0.747
Morphine				
Patient	37 (18.0)	8 (11.9)	29 (22.9)	0.083
Cumulative duration (day)	0	0	0 (0–1)	0.214
Fentanyl				
Patient	47 (31.3)	23 (34.3)	24 (28.9)	0.477
Cumulative duration (day)	0 (0–1)	0 (0–1)	0 (0–1)	0.369
Sedative	125 (83.3)	54 (80.6)	71 (85.5)	0.419
Midazolam				
Patient	80 (53.3)	38 (56.7)	42 (50.6)	0.456
Cumulative duration (day)	1 (0–2)	1 (0–1)	1 (0–3)	0.180
Propofol				
Patient	73 (48.7)	28 (41.8)	45 (54.2)	0.130
Cumulative duration (day)	0 (0–4.25)	0 (0–4)	1 (0–5)	0.891
Dexmedetomidine				
Patient	116 (77.3)	48 (71.6)	68 (81.9)	0.135
Cumulative duration (day)	3 (1–7)	2 (0–6)	3 (1–7)	0.253

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

Table 3. Main outcomes

Variable	Windowless (n=67)	Window (n=83)	P-value
Primary outcome			
Delirium incidence	29 (43.3)	18 (21.7)	0.005
Secondary outcome			
Delirium and coma-free day	0 (0–2)	0 (0–3)	0.105
Agitation	7 (10.4)	6 (7.2)	0.486
Mechanical ventilation	51 (76.1)	70 (84.3)	0.205
Ventilation-free days	2 (0-5)	2 (0–5)	0.615
Duration of mechanical ventilation	3 (0–7)	4 (2–7)	0.718
ICU LOS (day)	6 (3–11)	4 (6–12)	0.955
Hospital LOS (day)	36 (18–76)	37 (20–77)	0.670
ICU mortality	15 (22.4)	15 (18.1)	0.511
28-Day mortality	16 (23.9)	25 (30.1)	0.394

Values are presented as number (%) or median (interquartile range).
ICU: intensive care unit; LOS: length of stay.

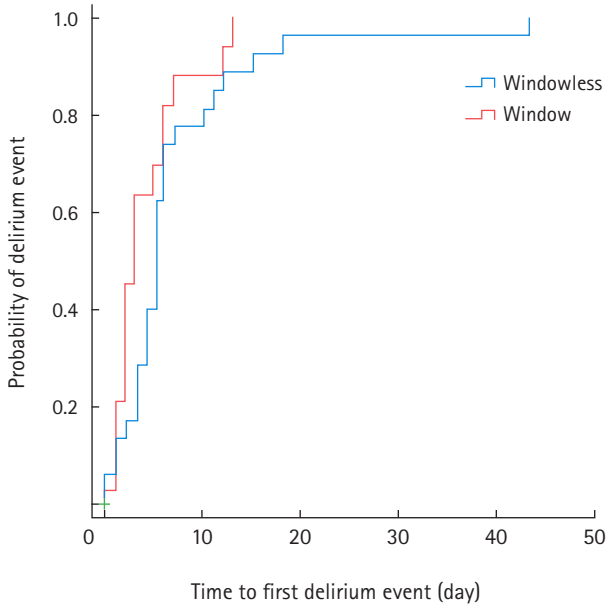
The main outcomes are listed in Table 3. The cumulative incidence of delirium throughout the whole cohort was 31.3% (47/150 patients), and the average duration of delirium and coma-free days in the whole cohort was 1.8 days. The cumulative incidence of delirium was significantly lower in the window group compared to that in the windowless group (21.7% vs. 43.3%; relative risk, 1.996; 95% CI, 1.220–3.265). The duration of delirium and coma-free days did not differ significantly between the two groups. The overall ICU and 28-day mortality rates were 20% and 27.4%, respectively, with no significant differences between the groups. The total ICU and hospital LOS were 10.5 and 49 days, respectively. Other secondary outcomes, including the number of mechanical ventilation-free days, ICU and hospital LOS, and mortality and 28-day mortality rates did not differ between the groups.

When comparing 47 patients with delirium, duration of delirium, the time of delirium onset after ICU admission and patients with agitation (RASS ≥+2) at the time of diagnosis were comparable between the two groups (Table 4). Diagnosis of delirium was mostly made by the attending physician (78.7%), followed by the administration of delirium medications (74.5%) (Supplementary Table 3).

Among the 47 patients with delirium, 35 (74.5%) were treated with antipsychotics during their ICU stay (Supplementary Table 4). Compared to the window group, patients in the windowless group were more likely to be administered antipsychotics for agitation episodes (82.8% vs. 61.1%) (Supplementary Table 4). Kaplan-Meier survival curves were used to estimate the time to first delirium event in the ICU and were compared using log-rank tests (Figure 1). There was no significant difference in the median onset time of the first delirium between the two groups. In Cox proportional regression analysis, admission to a room with windows was also not associated with a decreased risk of the time to first delirium event (adjusted HR, 0.526; 95% CI, 0.248–1.114) (Figure 2). In multivariate logistic regression analysis, admission to a room with windows was independently associated with a decreased risk of delirium (adjusted odds ratio, 0.318; 95% CI, 0.125–0.805) (Table 5).

DISCUSSION

This retrospective study consisted of patients with ICU stay for at least two consecutive days who were assigned single isolated room on either with window or without of the MICU. The patients staying in rooms without a window experienced a



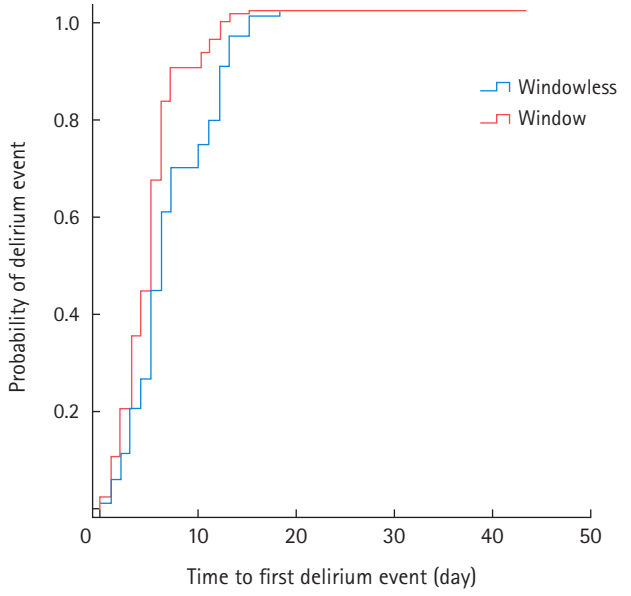
	Windowless	Window	All	Log-rank P-value
Onset time (day, median [IQR])	5 (3–7)	3 (2–6)	5 (2–6)	0.321

Figure 1. Unadjusted time to first delirium event. IQR: interquartile range.

Table 4. Delirium-related characteristics of both groups

Variable	All (n=150)	Windowless (n=67)	Window (n=83)	P-value
14-Day mortality	23 (15.3)	9 (13.4)	14 (16.9)	0.562
Duration of delirium (day)	1.6±0.3	2.2±0.5	1.2±0.4	0.125
Delirium and coma-free day	1.8±0.3	1.4±0.3	2.1±0.4	0.151
Unavailable and coma day	5.2±0.7	4.5±0.9	5.7±1.0	0.401
ICU LOS (day)	10.5±1.0	10.5±1.4	10.6±1.4	0.955
Onset of delirium after ICU admission (day)	1.7±0.4	2.8±0.8	0.8±0.3	0.016
Patients with RASS ≥+2 at the time of diagnosis[a]	20/47 (42.6)	12/29 (41.4)	8/18 (44.4)	0.016

Values are presented as number (%) or mean±standard error.
ICU: intensive care unit; LOS: length of stay; RASS: Richmond agitation sedation scale.
[a]Percentages were calculated in patients diagnosed with delirium.



	Coefficient	Adjusted HR (95% CI)[a]	P-value
Admission to window room	−0.643	0.526 (0.248–1.114)	0.093
Duration of administration of remifentanil (day)	−0.097	0.907 (0.837–0.983)	0.018
Duration of administration of dexmedetomidine (day)	−0.104	0.902 (0.833–0.976)	0.010

Figure 2. Cox-proportional hazard analysis. HR: hazard ratio; CI: confidence interval. [a]Variables associated in univariate analysis and tested in the multivariate model: age, alcohol abuse, hypoxic brain injury, medical history of steroid use, mechanical ventilation, duration of mechanical ventilator apply, self-extubation, vasoactive agents, duration of remifentanil administration, duration of midazolam administration, duration of propofol administration, and duration of dexmedetomidine administration.

Table 5. Factors associated with the incidence of delirium, multivariate logistic regression

Variable	Coefficient	Adjusted odds ratio[a]	P-value
Admission to a window room	−1.147	0.318 (0.125–0.805)	0.016

[a]Variables associated in univariate analysis and tested in the multivariate model and clinically relevant: age, alcohol abuse, hypoxic brain injury, medical history of steroid use, mechanical ventilation, duration of mechanical ventilator apply, self-extubation, vasoactive agents (norepinephrine, epinephrine, dopamine, dobutamine, vasopressin), duration of remifentanil administration, duration of midazolam administration, duration of propofol administration, and duration of dexmedetomidine administration.

higher incidence of delirium during their hospitalization. Additionally, admission to a windowed room appears to prevent occurrence of delirium.

Although circadian rhythms among critically ill patients are severely disrupted [20], the mechanism or pathogenesis of the association between light exposure and delirium remains poorly understood. One of the important mechanism of disrupted circadian rhythms in critically ill patients is decreased ascending reticular activating system (ARAS) activity [21]. Also, abnormalities in the functional connectivity of part of the ARAS have been observed during episodes of delirium [22,23]. Acetylcholine is the major neurotransmitters involved in activity of the ARAS function and is responsible for the increased levels of glutamate, dopamine, and norepinephrine [24,25] and decreased levels of serotonin and gamma-aminobutyric acid (GABA) [26,27] in the brain in the pathogenesis of delirium. In delirium, the loss of acetylcholine projections and dopaminergic overproduction from the ARAS result in disrupted alertness and attention compared to the normal circadian distribution of sleep-wakefulness conditions [28-30]. An increased synthesis of endogenous GABA agonists and stimulation by exogenous GABA agonists have been observed in delirium development [31,32]. Both benzodiazepines and propofol alter the effects of GABA in critically ill patients [33], either by typically increasing the total sleep time by prolonging stage 2 non-rapid eye movement (NREM), while suppressing REM [34], respectively, thus exacerbating sleep architecture [35]. The sleep-wake cycle is also affected by melatonin deficiency and irregular secretion. In critically ill patients, the normal response of melatonin secretion to shifts in light and darkness is disrupted, causing dysregulation of the melatonin secretion cycle or a change in the circadian clock phase in the suprachiasmatic nucleus [36].

Previous studies have suggested several possible explanations for the effects of exposure to natural light on delirium, as follows; First, emerging research suggests that circadian-rhythm-restoring interventions may improve health outcomes, including lower delirium rates, among critically ill patients. In a prospective before-after study, the incidence of delirium was lower compared with the new single-room ICU with daylight exposure and the ward-ICU without daylight exposure [18]. A retrospective study of postoperative ICU patients who underwent cardiac surgery [24] showed a higher incidence of delirium in spaces with wall-to-wall windows in a subgroup analysis of the age group 65 years and older than in a windowless space. The average age of all patients in our study was 66.7 years old, which is thought to have contributed to the development of delirium. Exposure to bright light, consolidated dark times at night, or melatonin agonists are common types of chronotherapy [37]. Although two studies from

Japan showed that artificial light therapy improved delirium prevalence or sleep and may have a role in preventing delirium [38,39], these effects require further validation; moreover, well-designed studies comparing the effect of natural light on delirium are lacking. A recent prospective study [40] and retrospective studies [41-43] were unable to demonstrate improved outcomes, including delirium associated with windowed ICU rooms. However, a lower mortality rate and shorter LOS were observed in patients admitted to the bright room of a cardiac ICU compared to those in patients admitted to a dark room [44]. Second, disorientation, loss of memory, hallucinations and delusions are more common in the windowless unit compared to the unit with windows and natural light [45]. Third, seasonal affective disorder and various depressive illness which been shown to be responsive to phototherapy [44,46] may also influence the development of delirium. Fourth, sensory deprivation is one of the risk factors of delirium and the presence of windows is associated with decrease in the occurrence of postoperative delirium by preventing sensory deprivation [26,28]. Furthermore, windows and light may also be associated with reduction in physical stress and pain shown in patients undergoing elective spine surgery [47]. Patients staying on the bright side not only required 22% fewer opioid analgesics during their hospitalization, but also reported significantly less perceived stress.

In the present study, admission to a room with windows reduced the incidence of delirium. After adjustment of confounding variables, this result was still significant. As far as we know, this is the first study to show this association in a MICU environment. However, no differences in delirium and coma-free days were observed between the windowless and window group. There are two possible explanations. Although clinically insignificant, the duration of coma days was longer in the window group compared with windowless group (5.7±1.0 days vs. 4.5±0.9 days, P=0.401). Also, 14-day mortality was slightly higher in the window group compared to the windowless group (16.9% vs. 13.4%, P=0.562) and as defined in our study, days without delirium and coma were counted as zero if death occurred within 14 days of admission to the ICU.

This study has several limitations. First, as this study only included patients from the MICU of a university-affiliated hospital, these results may not be generalizable to other critically ill patients. However, we believe that this study population of patients with a high risk of delirium may benefit most from measures to prevent delirium. It is important to investigate the value of noninvasive, nonpharmacologic measures to prevent delirium, such as natural light, in high-risk populations. Second, patients were screened for delirium once a day using CAM-ICU. Considering the intraday variability of delirium and changes in the patient's condition there is a possibility that delirium may have been underestimated. Therefore, delirium was diagnosed by comprehensively evaluating composite factors (including three factors along with CAM-ICU) to overcome this limitation. Several studies have also used additional criteria for assessment of delirium including treatment with haloperidol [48], evaluation of medical and nursing charts or documentation for keywords associated with delirium [13,18]. Third, due to the observational study design, it is difficult to discern the exact mechanism of the effect of windows in an ICU room. This study is not able to distinguish the effect of nature of the light, regularity of light exposure, or continuous sensory input. Fourth, there were also disparities between the two groups. Previous antipsychotic use was more frequent in the window group and there were more patients with chronic liver disease in the windowless group. It is unclear how these differences affected the outcome. However, there were no differences in other important known risk factors affecting delirium, such as age and illness severity. Because all patients were admitted to isolation rooms, noise exposure was minimized. During the night time, the lights are dimmed to half of its brightness unless the patient is in a critical condition. Moreover, multicomponent ABCDEF bundles has been implemented in our ICU to reduce or prevent delirium. There were no changes in doctor-patient or nurse-patient ratios, nor in practice or protocols for sedation, analgesia, and the arrangement of medical equipment during the study period. Exposure to natural light through windows was associated with a decreased risk of delirium as compared to admission to a single windowless room.

CONFLICT OF INTEREST

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

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Conceptualization: HJL, JL. Data curation: HJL, EB. Formal analysis: HJL, JL. Methodology: HJL, HYL, JL, SML. Project administration: HJL, JL. Visualization: HJL, JL. Writing–original draft: HJL, JL. Writing–review & editing: HJL, JL.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4266/acc.2021.00556.

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Supplementary Table 1. Reflective measurement (lux)

	Windowless	Window	P-value
10A	892.75 (819.375–922.875)	1,143.24 (1,092.375–1,267.75)	<0.001
2P	908.25 (824.75–923.125)	1,316 (1,237.5–1,455.875)	<0.001
6P	909.75 (817.75–929.125)	1,030.5 (991.5–1,091.125)	0.001
All	904.75 (838.125–921.375)	1,143.25 (1,074.625–1,280)	<0.001

Illuminance measured at different hours of the day in rooms with windows or without windows.
The digital light meter used was LUX HiTESTER 3423 manufactured by HIOKI.

Supplementary Table 2. Univariable logistic regression analysis

Variable	OR	95% CI	P-value
Admission to a light room	0.363	0.178–0.739	0.005
Age	1.006	0.984–1.029	0.58
Sex	1.509	0.753–3.027	0.245
Body mass index	0.961	0.890–1.038	0.308
Smoking			0.095
Ever	0.365	0.113–1.179	0.092
Alcohol abuse	2.374	0.988–5.702	0.053
Underlying disease			
Hypertension	1.243	0.623–2.481	0.536
Diabetes mellitus	1.041	0.520–2.085	0.91
Chronic liver disease	0.698	0.238–2.050	0.512
Chronic kidney disease	0.594	0.270–1.306	0.193
Cardiovascular disease	0.9	0.425–1.905	0.783
Cerebrovascular disease	0.865	0.257–2.914	0.815
Cognitive disorder	0.725	0.073–7.155	0.782
Chronic obstructive pulmonary disease	0.725	0.073–7.155	0.782
Hypoxic brain injury	0.664	0.590–0.747	0.027
ICU admission diagnosis			
Respiratory failure	1.73	0.816–3.665	0.151
Sepsis	1.793	0.752–4.276	0.185
Renal replacement therapy	0.571	0.214–1.525	0.26
Cardiogenic cause	0.539	0.203–1.432	0.21
Hypovolemic shock	0.981	0.954–1.008	0.336
Post operation care	0.981	0.954–1.008	0.336
Trauma			
Other	0.996	0.325–3.047	0.994
APACHE II score	0.97	0.932–1.010	0.134
SOFA	0.944	0.869–1.025	0.17
SAPS II	0.995	0.978–1.012	0.581
Mechanical ventilation	1.965	0.742–5.204	0.169
Duration of mechanical ventilation (day)	1.03	0.999–1.062	0.058
Duration of mechanical ventilation free day	1.057	0.989–1.129	0.104
Medical history			
Antipsychotics	1.633	0.490–5.440	0.421
Benzodiazepine	2.078	0.706–6.117	0.177
Hypnotics	2.007	0.635–6.339	0.228
Steroid	2.117	1.014–4.421	0.044
Alcohol abuse	0.426	0.048–3.752	0.429
Use of opioids and hypnotics			
Duration of morphine administration (day)	0.975	0.761–1.250	0.841
Duration of remifentanil administration (day)	1.044	1.009–1.081	0.014
Duration of fentanyl administration (day)	0.981	0.625–1.540	0.933
Duration of midazolam administration (day)	1.079	0.941–1.237	0.277
Duration of propofol administration (day)	1.038	1.005–1.078	0.047
Duration of dexmedetomidine administration (day)	1.034	0.9997–1.069	0.052

(Continued to the next page)

Supplementary Table 2. Continued

Variable	OR	95% CI	P-value
Opioid	1.643	0.650–4.153	0.291
Sedative	0.964	0.383–2.422	0.937
Vasoactive agents			
Norepinephrine	1.095	0.527–2.276	0.808
Epinephrine	3.248	1.129–9.345	0.023
Dopamine	0.539	0.203–1.432	0.21
Dobutamine	0.725	0.073–7.155	0.782
Vasopressin	1.546	0.659–3.625	0.314
Renal replacement therapy	0.681	0.329–1.410	0.3
ECMO	0.824	0.276–2.462	0.729
Self-extubation	1.098	0.097–12.416	0.94
Hospital LOS	1.016	1.006–1.026	0.001
ICU LOS	1.039	1.008–1.070	0.013

APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sepsis Organ Failure Assessment; SAPS: Simplified Acute Physiology Score; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; LOS: length of stay.

Supplementary Table 3. Composite factors for assessment of delirium

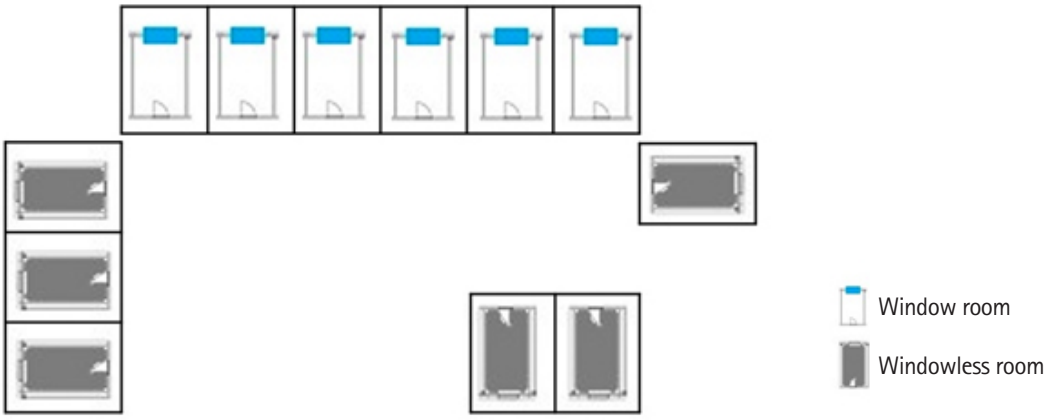
Variable	All (n=47)	Windowless (n=29)	Window (n=18)	P-value
CAM-ICU	24 (51.1)	14 (48.3)	10 (55.6)	0.627
Clinician suspicion	37 (78.7)	21 (72.4)	16 (88.9)	0.18
Psychiatric consultation	28 (59.6)	13 (44.8)	15 (83.3)	0.009
Delirium medication	35 (74.5)	15 (51.7)	7 (38.9)	0.391

Values are presented as a number (%).
CAM-ICU: confusion assessment method for the intensive care unit.

Supplementary Table 4. Treatment of delirium in the ICU

Variable	All (n=47)	Windowless (n=29)	Window (n=18)	P-value
Treatment, patients	35 (74.5)	24 (82.8)	11 (61.1)	0.098
Lorazepam				
Patient	32 (68.1)	21 (72.4)	11 (61.1)	0.419
Cumulative duration (day)	1 (0–2)	1 (0–1.5)	1 (0–4.5)	0.45
Quetiapine				
Patient	14 (29.8)	6 (20.7)	8 (44.4)	0.083
Cumulative duration (day)	0 (0–1)	0	0 (0–4.3)	0.459
Haloperidol				
Patient	14 (29.8)	9 (31.0)	5 (27.8)	0.812
Cumulative duration (day)	0 (0–1)	0 (0–1)	0 (0–4)	0.393
Alprazolam				
Patient	3 (6.4)	1 (3.4)	2 (11.1)	0.296
Cumulative duration (day)	0	0	0	0.307
Melatonin				
Patient	6 (12.8)	3 (10.3)	3 (16.7)	0.528
Cumulative duration (day)	0	0	0	0.312

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



Supplementary Figure 1. The layout of the medical intensive unit.

Supplementary Figure 2. Pictures of rooms with and without windows.

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How do physicians and nurses differ in their perceived barriers to effective enteral nutrition in the intensive care unit?

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Background: Patients hospitalized in intensive care units are susceptible to chronic malnutrition from changes in protein and energy metabolism in response to trauma. Therefore, nutritional support, especially enteral nutrition, is one of the most important treatment measures for these patients. However, there are several barriers in the hospitals in treating patients with enteral nutrition. This study was performed to compare the perceptions of care providers (physicians and nurses) on the barriers to enteral nutrition in intensive care units.

Methods: This was a cross-sectional descriptive and analytic study. This study included 263 nurses and 104 physicians in the intensive care units of Kerman University of Medical sciences, in south east of Iran. A questionnaire of enteral nutrition barriers in intensive care units was used. IBM SPSS ver. 19 was used to analyze data.

Results: There was a significant difference between the two groups in the three subscales of intensive care units (P=0.034), dietician support (P<0.001) and critical care provider attitudes and behavior (P=0.031). There was also a significant difference between having completed educational courses and the score of enteral nutrition barriers in the two groups (P<0.05); the people who received an educational course had a better perception of enteral nutrition barriers.

Conclusions: Physicians and nurses agreed with the perception of enteral nutrition barriers, but there was a difference in their perception on some barriers. Strategies such as in-service training and increasing the knowledge and skills of physicians and nurses can reduce these differences.

Key Words: critical care; enteral nutrition; intensive care; intensive care units; nurse; physician

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INTRODUCTION

Nutrition plays an important role in patients with a chronic and acute condition, but some of these patients cannot feed themselves because of metabolic stress and/or being in an unconscious state. Without proper nutritional support, these patients are at serious risk for malnutrition [1-3]. Impaired immune function, increased risk of sepsis, and weakening of respiratory muscles are some of the outcomes of malnutrition that can result in extended use of a mechanical ventilation machine [4]. Enteral nutrition involves administering nutrients by nasogastric, oral-gastric, or percutaneous tubes into the duodenum or jejunum and is a suitable strategy for patients hospitalized in intensive care units [5-9]. Enteral nutrition should

be the first and foremost nutrition therapy in patients whose gastrointestinal tract is functioning well. Despite the importance of enteral nutrition in intensive care units, this method is associated with some obstacles [8].

Several types of factors prevent the implementation of recommended guidelines in clinical practice, such as those related to individuals, social issues, and organizations [10]. Understanding these barriers helps to identify the gap between recommended guidelines and practices and enables the development of strategies to overcome these barriers [11,12]. The researchers reported that patients receive on average less than 60% of their prescribed calories and protein [13].

A literature review on enteral nutrition revealed the gap between the recommendations of evidence-based guidelines and what is achieved in intensive care units [11,12,14,15]. A qualitative analysis, using interviews with nutritionists, physicians, and nurses, identified several barriers to adequate nutrition in the intensive care units, such as guidelines, implementation process, institutional factors, individual provider behavior, and patient clinical conditions [16]. In another study, the most important barriers included an insufficient supply of feeding pumps, insufficient enteral formula in the unit, and difficulties in obtaining small bowel access in patients that do not tolerate enteral nutrition [11]. Views and attitudes of medical and nursing practitioners in Australia on the barriers to nutrition intervention in intensive care units showed that there are competing priorities when caring for patients, and the implementation of nutrition therapy is influenced by the practitioner roles and expectations [15]. A study in England reported that only half of the patients under intensive care received the necessary nutrients. Some reasons for this included a delay in the start and prescription of enteral nutrition, disconnection of nutrition due to surgical and diagnostic procedures, gastrointestinal intolerance, and no standard protocol of enteral nutrition for nurses [14].

Barriers can vary based on the different sites, local context, and available facilitators in hospitals [17]. This indicates that the effect of each barrier differs according to profession, supporting the need to better understand the barriers faced by each profession and how the barriers differ according to the context [7,10]. In addition, some barriers may be common across intensive care units, but the frequency and magnitude of these barriers may differ due to the unique elements of the local context and available facilitators. Therefore, critical care providers have to be aware of enteral nutrition barriers [13]. This study aimed to compare the views of nurses and physicians on enteral nutrition barriers in the intensive care units of hospitals Kerman University of Medical sciences.

KEY MESSAGES

- By identifying the barriers to enteral nutrition in patients admitted to intensive care units, it is possible to plan, implement and prevent complications in these patients.
- Awareness of the treatment team's perspective can increase optimal nutritional care of the intensive care patients.
- Reducing the difference between the perceptions of physicians and nurses plays an important role in removing enteral nutrition barriers and providing appropriate enteral nutrition in intensive units.

MATERIALS AND METHODS

Ethical Statement

This study was approved by the Ethics and Research Committee of Kerman University of Medical Sciences (No. IR.Kmu.REC. 1396, 1665), After obtaining the necessary permits, the researcher referred to the study setting at different shift works and coordinated with participants for the study. After specifying eligible participants, sufficient information about study aims, their importance, and confidentiality was provided for participants. The researcher tried not to refer during rush hours and visiting hours in the department to prevent any interference in patients' treatment process and also to ensure that all participants were mentally ready and had enough time to answer the questionnaire. The questionnaires were given to the participants and then delivered after completion.

Study Design and Setting

This descriptive-analytical cross-sectional study was conducted on intensive care units of teaching hospitals affiliated to Kerman University of Medical Sciences University of Medical Sciences. These centers are among the largest ones in in south east of Iran. This study lasted from May to July 2020.

Sample Size and Sampling

The study population consisted of 110 physicians and 270 nurses working in intensive care units in 2020. The inclusion criteria for nurses included a B.S or higher degree, while the inclusion criteria for physicians included a specialty or higher degree. Overall, 104 physicians and 263 nurses participated in

the study, and the response rate was 94.5% for physicians and 97.4% for nurses.

Instrument

A demographic information form and questionnaire on the barriers to delivery of enteral nutrition were used. The form collected demographic and background information including age, sex, marital status, work experience, and work experience in an intensive care unit.

The barriers to the delivery of enteral nutrition questionnaire developed by Cahill et al. [18] in the U.S. consisted of 26 items and five dimensions. The five dimensions are as follows. (1) "Guideline recommendations and implementation strategies" includes: I am not familiar with our current guidelines for nutrition in the intensive care unit, current scientific evidence supporting some nutrition interventions is inadequate to inform practice, the language of the recommendations of the current guidelines for nutrition are not easy to understand, the current guidelines for nutrition are not readily accessible when I want to refer to them, no feeding protocol in place to guide the initiation and progression of enteral nutrition, and current feeding protocol is outdated. (2) "Intensive care unit resources" includes: not enough nursing staff to deliver adequate nutrition, enteral formula not available on the unit, and no or not enough feeding pumps on the unit. (3) "Dietician support" includes: waiting for the dietitian to assess the patient, dietitian not routinely present on weekday patient rounds, no or not enough dietitian coverage during evenings, weekends and holidays, and not enough time dedicated to education and training on how to optimally feed patients. (4) "Delivery of enteral nutrition" includes: delay in physicians ordering the initiation of enteral nutrition, waiting for physician/radiology to read x-ray and confirm tube placement, frequent displacement of feeding tube, requiring reinsertion, delays in initiating motility agents in patients not tolerating enteral nutrition (i.e. high gastric residual volumes), delays and difficulties in obtaining small bowel access in patients not tolerating enteral nutrition (i.e. high gastric residual volumes), in resuscitated, hemodynamically stable patients, other aspects of patient care still take priority over, and nutrition therapy not routinely discussed on patient care rounds. (5) "Critical care provider attitudes and behavior" includes: non-intensive care unit physicians (i.e. surgeons, gastroenterologists) requesting patients not be fed enterally, nurses failing to progress feeds as per the feeding protocol, feeds being held due to diarrhea, fear of adverse events due to aggressively feeding patients, feeding being held too far in advance of procedures or operating room visits, and general belief among intensive care unit team that provision of adequate nutrition does not impact on patient outcome. The 5-point Likert scale was used and included the following: not at all important (score=1), somewhat unimportant (score=2), neither important nor unimportant (score=3), somewhat important (score=4), and very important (score=5). The minimum and maximum scores were 26 and 130, respectively. The content validity index was determined (0.92) and the Cronbach's alpha coefficient was calculated to be 0.81.

Data Analysis

Data were analyzed using IBM SPSS ver. 20 (IBM Corp., Armonk, NY, USA). Descriptive statistics such as frequency, percentage, mean, standard deviation, and inferential statistics such as independent t-test and analysis of variance were used in this study. Kolmogorov-Smirnov test was used to investigate the normal data distribution in each of the measurements. The significance level was set at 0.05.

RESULTS

In the overall participant group (263 nurses and 104 physicians), most nurses were female (87.5%) and most physicians were male (88.5%, P=0.001). Most nurses were 31–40 years old (41.4%), and most physicians were 41–50 years old (69.2%) (P=0.001). The majority of participants among both nurses (76.6%) and physicians (99%) were married (P=0.001). The clinical work experience of both nurses (33.7%) and physicians (36.9%) was 6–10 years (P=0.67). Most nurses had 1–5 years of work experience in intensive care units (49.6%), while most physicians had 6–10 years in these units (35.6%) (P=0.001). Most physicians passed an educational course on the nutrition of patients (84.6%), while the majority of nurses had not received such a course (70.0%) (P=0.001) (Table 1).

From the perspective of physicians, the barriers to enteral nutrition were dietician support, resources, guideline recommendations, implementation strategies, delivery of enteral nutrition to the patient, and critical care provider attitudes and behavior. From the perspective of nurses, guideline recommendations and implementation strategies, dietician support, resources, delivery of enteral nutrition to the patient, and critical care provider attitudes and behavior were the barriers to enteral nutrition. Although the mean total score of enteral nutrition barriers from the perspective of nurses was less than that of physicians, the difference was not statistically signifi-

Table 1. Comparison of the demographic characteristics of physicians and nurses in ICUs

Characteristics	Physician	Nurse	Chi-square test	P-value
Sex			191.23	0.001
Female	12 (11.5)	230 (87.5)		
Male	92 (88.5)	33 (12.5)		
Age (yr)			186.58	0.001
20–30	2 (1.9)	103 (39.2)		
31–40	5 (4.8)	109 (41.4)		
41–50	72 (69.2)	21 (8.0)		
>50	25 (24.0)	30 (11.4)		
Marital status			26.22	0.001
Single	2 (1.9)	62 (23.6)		
Married	102 (98.1)	201 (76.4)		
Clinical work experience (yr)			1.56	0.67
0–5	27 (26.0)	86 (32.7)		
6–10	38 (36.5)	88 (33.5)		
11–15	25 (24.0)	57 (21.7)		
>15	14 (13.5)	32 (12.2)		
Work experience in ICU (yr)			15.56	0.001
1–5	32 (30.8)	128(48.7)		
6–10	36 (34.6)	87 (33.1)		
11–15	21 (20.2)	35 (13.3)		
>15	15 (14.4)	13 (5.0)		
Educational course of nutrition for patients			89.52	0.001
Yes	88 (84.6)	79 (30.0)		
No	16 (15.4)	184 (70.0)		

Values are presented as number (%).
ICU: intensive care unit.

Table 2. Comparison of the perceived mean scores of enteral nutrition barriers in physicians and nurses in ICUs

Subscale of enteral nutrition barriers	Nurse	Physician	t-test	P-value
Guideline recommendations and implementation strategies	3.91±0.05	3.77±0.10	1.27	0.205
ICU resources	3.80±0.05	3.98±0.11	−1.39	0.026
Dietician support	3.90±0.05	4.60±0.04	−9.41	<0.001
Delivery of enteral nutrition to the patient	3.66±0.05	3.50±0.05	2.24	0.165
Critical care provider attitudes and behavior	3.52±0.05	3.33±0.04	2.71	0.007
Total	3.74±0.68	3.75±0.04	−0.18	0.855

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

cant (P=0.855).

Among the subscales of enteral nutrition barriers, there was a significant difference among the two groups in the three subscales of resources (P=0.026), dietician support (P<0.001), and critical care provider attitudes and behavior (P=0.007). Regarding resources and dietician support, the highest score was from physicians; regarding critical care provider attitudes and behavior, the highest score was from nurses. There was no significant difference between the perspectives of physicians and nurses in guideline recommendations and implementation strategies and delivery of enteral nutrition to the patient (Table 2).

In the case of guideline barriers, the mean score of four questions (including: I am not familiar with our current guidelines for nutrition in the intensive care unit, current scientific

evidence supporting some nutrition interventions is inadequate to inform practice, the language of the recommendations of the current guidelines for nutrition are not easy to understand, and current feeding protocol is outdated) were significantly higher for nurses than physicians. However, in two questions (including: the current guidelines for nutrition are not readily accessible when I want to refer to them and no feeding protocol in place to guide the initiation and progression of enteral nutrition), the mean score in physicians was significantly higher than in nurses (P<0.05). In the case of resource barriers, the mean score of the question "no or not enough feeding pumps on the unit" was significantly higher in physicians than in nurses (P<0.05). In the case of nutritionist barriers, the mean score of all questions (including: waiting for the dietitian to assess the patient, dietitian not routinely present on weekday patient rounds, no or not enough dietitian coverage during evenings, weekends and holidays, and not enough time dedicated to education and training on how to optimally feed patients) was significantly higher in physicians than in nurses (P<0.05). Regarding barriers to enteral nutrition delivery, the mean score of three questions (including: delay in physicians ordering the initiation of enteral nutrition, waiting for physician/radiology to read X-ray and confirm tube placement, and frequent displacement of feeding tube, requiring reinsertion) was significantly higher in nurses than physicians; for the other three questions (including: delays and difficulties in obtaining small bowel access in patients not tolerating enteral nutrition (i.e. high gastric residual volumes), in resuscitated, hemodynamically stable patients, other aspects of patient care still take priority over, and nutrition therapy not routinely discussed on patient care rounds), the mean score of physicians was significantly higher than nurses (P<0.05). Regarding the barriers related to nutritional attitude, the mean score of three questions (including: non-intensive care unit physicians (i.e., surgeons, gastroenterologists) requesting patients not be fed enterally, nurses failing to progress feeds as per the feeding protocol, and general belief among intensive care unit team that provision of adequate nutrition does not impact on patient outcome) was significantly higher in nurses than physicians, while for the other three questions (including: feeds being held due to diarrhea, fear of adverse events due to aggressively feeding patients, and feeding being held too far in advance of procedures or operating room visits), the mean score of physicians was significantly higher than physicians (P<0.05) (Table 3).

These results showed that there was a significant relationship between the mean score perceived by physicians and nurses and the educational course. The mean score perceived by physicians and nurses who passed the educational course was significantly higher (P<0.05).

DISCUSSION

The results of this study showed that the perceived mean total score of enteral nutrition barriers from the perspective of nurses was lower than that of physicians, but this difference was not statistically significant. These results indicated that the perception and scoring of enteral nutrition barriers of both physicians and nurses were in agreement, which was consistent with the results of Chapple et al [15].

Based on the current results, physicians were considerably more aware of the importance of resources in the intensive care units such as no or not enough feeding pumps on the unit. Therefore, the restriction of resources can be a big barrier for critical care providers to follow guideline recommendations. Consistent with this result, Shayesteh et al. [17] reported that one of the barriers to enteral nutrition was sufficient resources and facilities. For example, in Iran, providing ICU resources imposes high expenses on patients. Lack of budget and insufficient facilities will affect the quality of treatment in intensive care units.

Physicians assigned a higher score to all questions related to nutritionist barriers to dietician support, meaning that from the perspective of physicians, a lack of dietician support can be a big barrier to proper nutrition for intensive care patients. Most physicians indicated that a lack of dietician support can be an important barrier for the proper nutrition of patients hospitalized in intensive care units, and this is consistent with the results of Shayesteh et al. [17]. In addition, a study at Hummer Smith hospital in London showed that dietician support in the intensive care units is so critical that nutrition consultation and diet therapy strategies in these patients lead to a decrease in malnutrition and improvement of weight gain [19]. The American Society for Parenteral Enteral Nutrition stated that dietician support is vital for recovery, an increase of safety, and a decrease of treatment expenses. Hospital managers should take into account nutrition consultation for proper enteral nutrition [20]. Chapple et al. [15] also emphasized the role of dieticians along with physicians and nurses in proper enteral nutrition for patients hospitalized in intensive care units.

Based on the current results, the mean score of critical care provider attitudes and behaviors (such as a request from

Table 3. Comparison of questions of enteral nutrition barriers in physicians and nurses in ICUs

Subscale	Question of enteral nutrition barriers	Nurse	Physician	t-test	P-value
Guideline recommendations and implementation strategies	I am not familiar with our current guidelines for nutrition in the ICU.	4.06±0.06	3.81±0.11	1.85	0.060
	Current scientific evidence supporting some nutrition interventions is inadequate to inform practice.	3.80±0.68	3.50±0.12	2.22	0.020
	The language of the recommendations of the current guidelines for nutrition are not easy to understand.	3.65±0.07	3.22±0.11	3.24	0.001
	The current guidelines for nutrition are not readily accessible when I want to refer to them.	3.95±0.06	4.31±0.12	−2.77	0.006
	No feeding protocol in place to guide the initiation and progression of enteral nutrition	4.04±0.06	4.34±0.12	−2.27	0.023
	Current feeding protocol is outdated.	3.94±0.06	3.46±0.13	3.62	0.001
ICU resources	Not enough nursing staff to deliver adequate nutrition	3.39±0.08	3.27±0.15	0.70	0.487
	Enteral formula not available on the unit	4.06±0.06	4.27±0.12	−1.57	0.117
	No or not enough feeding pumps on the unit	3.94±0.07	4.40±0.12	−3.09	0.002
Dietitian support	Waiting for the dietitian to assess the patient	3.98±0.06	4.43±0.61	−3.83	0.002
	Dietitian not routinely present on weekday patient rounds	3.95±0.06	4.60±0.05	−5.87	0.001
	No or not enough dietitian coverage during evenings, weekends and holidays	3.85±0.07	4.75±0.06	−7.10	0.001
	Not enough time dedicated to education and training on how to optimally feed patients	3.80±0.07	4.61±0.07	−6.41	0.001
Delivery of enteral nutrition to the patient	Delay in physicians ordering the initiation of enteral nutrition	3.77±0.06	2.57±0.12	9.10	0.001
	Waiting for physician/radiology to read X-ray and confirm tube placement	3.41±0.08	2.63±0.08	5.67	0.001
	Frequent displacement of feeding tube, requiring reinsertion	3.06±0.09	1.85±0.09	7.28	0.001
	Delays in initiating motility agents in patients not tolerating enteral nutrition (i.e., high gastric residual volumes)	3.71±0.07	3.76±0.09	−0.49	0.622
	Delays and difficulties in obtaining small bowel access in patients not tolerating enteral nutrition (i.e., high gastric residual volumes)	3.97±0.06	4.64±0.07	−6.86	0.001
	In resuscitated, hemodynamically stable patients, other aspects of patient care still take priority over	3.88±0.07	4.58±0.07	−6.61	0.001
	Nutrition therapy not routinely discussed on patient care rounds	3.81±0.07	4.45±0.07	−5.90	0.001
Critical care provider attitudes and behavior	Non-ICU physicians (i.e., surgeons, gastroenterologists) requesting patients not be fed entirely	3.39±0.07	2.15±0.14	7.55	0.001
	Nurses failing to progress feeds as per the feeding protocol	3.25±0.08	2.55±0.13	4.57	0.001
	Feeds being held due to diarrhea	3.69±0.06	4.31±0.05	−6.81	0.001
	Fear of adverse events due to aggressively feeding patients	3.58±0.07	4.22±0.06	−6.64	0.001
	Feeding being held too far in advance of procedures or operating room visits	3.96±0.07	4.71±0.06	−7.57	0.001
	General belief among ICU team that provision of adequate nutrition does not impact on patient outcome	3.25±0.08	2.04±0.09	9.90	0.001

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

non-intensive care physicians for no need for enteral nutrition, the inability of nurses to promote enteral nutrition, according to the nutritional protocol, and the general belief of care providers that providing proper nutrition does not affect the patient's recovery) was significantly higher for nurses than that of physicians. This result indicates that nurses had a better understanding that incomplete awareness or negative attitude of critical care providers towards guideline recommendations might lead not to following the prescribed instructions and the patient would suffer from the side effects. The understanding of this fact may be from nurses' experience of inappropriate actions of nurses and physicians regarding nutrition and

lack of nutrition guidelines. Chan et al. [21] investigated the performance of 1,203 nurses for tube placement verification, management of high gastric residual volume, and response to nutritional side effects. The results showed that nurses did not have sufficient knowledge and efficiency in tube feeding [21]. Several studies showed that one of the important barriers to enteral nutrition was the poor performance of care providers and the lack of a system to evaluate their performance [22,23]. However, Mehrnosh et al. [24] reported that the nurses' performance for tube feeding was at an average level and considered the accreditation time of hospitals as the reason for the relative improvement in the performance.

Although nurses and physicians differed on some questions in this study, they did not differ significantly overall. There was no significant difference among the perspectives of physicians and nurses in guideline recommendations and implementation strategies and delivery of enteral nutrition to the patient so that the two groups agreed that features of guideline recommendations and methods chosen for their implementation could interfere with their applicability. For example, format, writing, availability, and being up-to-date are issues that may challenge critical care providers. Several studies have confirmed these results. The two groups also agreed that delivery of enteral nutrition to patients could be a barrier to enteral nutrition, meaning that the patient's status plays a role in successfully applying nutrition guidelines and implementing nutrition guidelines for chronic patients may be more difficult. For example, resuscitation or stabilization of hemodynamic status is more preferred than nutrition, and sometimes there will be a gap between the clinic and their knowledge. In this regard, a study by Cahill et al. [11] in North America stated that the most important nutrition barriers from the perspective of nurses were the gap between evidence-based clinical guidelines and what is done in practice.

The mean score of the perceived enteral nutrition barrier was significantly higher in physicians and nurses who passed educational courses, indicating that training had a vital role in increasing the perception of barriers to enteral nutrition. Consistent with these results, Darawad et al. [25] reported that education, the Internet, and nursing faculty were the main sources of enteral nutrition knowledge for nurses, and the authors concluded that awareness of responsibility, backup documentation system, and recording current enteral nutrition could be effective to improve the perception of enteral nutrition barriers and its function. Several studies confirmed this finding [13,22,25].

This study had some limitations. First, the study included a low number of physicians. Second, the participants' data were evaluated by a self-reported questionnaire. Therefore, a larger sample should be used in future studies to improve potential generalizability.

Since perceived enteral nutrition barriers in intensive care units have been reported at an average level for care providers, and while the providers overall showed agreement in the perception and scoring of enteral nutrition barriers, there was a difference in perception between physicians and nurses on some barriers. This suggests that clarifying the reasons for these differences may help establish strategies such as in-service training to increase the knowledge and skills of physicians and nurses and reduce these differences. The cooperation of the treatment team including physicians and nurses is critical in playing an important role to remove these barriers and provide effective enteral nutrition. Deficiency in clinical guideline recommendations, resources, dietician support, delivery of enteral nutrition to the patient, critical care provider attitudes and behavior are considered as enteral nutrition barriers that negatively affect the quality of. Therefore, critical care providers' behavior and attitude towards proper enteral nutrition may be encouraged by providing sufficient resources, proper clinical guidelines, intra-professional cooperation, and continual training. This investigation should also be explored in other populations. Identifying and overcoming the barriers to enteral nutrition in patients in intensive care units will help prevent complications in these patients and improve patient care.

CONFLICT OF INTEREST

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

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Outcomes of critically ill patients according to the perception of intensivists on the appropriateness of intensive care unit admission

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Background: It is important for intensivists to determine which patient may benefit from intensive care unit (ICU) admission. We aimed to assess the outcomes of patients perceived as non-beneficially or beneficially admitted to the ICU and evaluate whether their prognosis was consistent with the intensivists' perception.

Methods: A prospective observational study was conducted on patients admitted to the medical ICU of a tertiary referral center between February and April 2014. The perceptions of four intensivists at admission (day 1) and on day 3 were investigated as non-beneficial admission, beneficial admission, or indeterminate state.

Results: A total of 210 patients were enrolled. On days 1 and 3, 22 (10%) and 23 (11%) patients were judged as having non-beneficial admission; 166 (79%) and 159 (79%), beneficial admission; and 22 (10%) and 21 (10%), indeterminate state, respectively. The ICU mortality rates of each group on day 1 were 59%, 23%, and 59%, respectively; their 6-month mortality rates were 100%, 48%, and 82%, respectively. The perceptions of non-beneficial admission or indeterminate state were the significant predictors of ICU mortality (day 3: odds ratio [OR], 4.049; 95% confidence interval [CI], 1.892–8.664; P<0.001) and 6-month mortality (day 1: OR, 4.983; 95% CI, 1.260–19.703; P=0.022; day 3: OR, 4.459; 95% CI, 1.162–17.121; P=0.029).

Conclusions: The outcomes of patients perceived as having non-beneficial admission were extremely poor. The intensivists' perception was important in predicting patients' outcomes and was more consistent with long-term prognosis than with immediate outcomes. The intensivists' role can be reflected in limited ICU resource utilization.

Key Words: critical care outcomes; critical illness; intensive care units; medical futility; patient admission; perception

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INTRODUCTION

Advances in intensive care unit (ICU) treatment have led to improved survival of patients with critical illness. However, negative outcomes despite the provision of life-sustaining care can cause distress to patients and family members, inappropriate distribution of medical

resources [1,2], burnout of ICU staff [3,4], and harm to other patients [5]. Thus, it is important for ICU physicians to distinguish which patient could benefit from ICU admission [6]. Knowing whose admission would be beneficial could help decide the priority of ICU admission, the level of treatment, and the distribution of medical resources.

In Asian countries, it is generally a taboo to discuss death with the individual directly involved. Particularly in the Confucianism cultural areas, including Korea, the notion of filial duties dissuades the family members of seriously ill patients from signing advance care directives, even if patients' conditions are irreversible or critical. Therefore, there has been scarce effort to investigate the appropriateness of ICU admission. We believe that the Korean society will probably face the issue of distributive justice of medical resources, considering increasing longevity, increasing compromised hosts, and restraint from government health insurance service.

Until recently, ICU treatment [7] was regarded as largely inappropriate when the patient has irreversible severe neurologic injuries or in cases in which physicians, nurses, and healthcare staff agree that the patient will not survive outside the acute care setting [8,9]. However, a concrete definition of beneficial or non-beneficial treatment/admission in the ICU does not exist. Therefore, the aim of this study was to evaluate the outcomes of critically ill patients according to the early perception of intensivists and to investigate whether the perception of ICU physicians can be a predictor of the prognosis of patients admitted to the ICU.

KEY MESSAGES

- The intensivists' perception of the appropriateness of intensive care unit (ICU) admission was consistent with the patients' ICU outcomes and long-term prognosis.
- Judgment according to the expertise of critical care specialists is meaningful for the evaluation of medical futility or non-beneficial admission.
- The role of intensivists can be reflected from the viewpoint of allocating limited resources at high cost in the ICU.

MATERIALS AND METHODS

Ethics Statement

This study was approved by the Institutional Review Board of Asan Medical Center (IRB No. 2014-0038) and waived the informed consents due to the nature of the study.

Study Design

This prospective observational study was conducted at a tertiary referral center located in Seoul, Korea. Its 28-bed semi-closed medical ICU is run by four full-time intensivists (all with more than 10 years of experience excluding the training period), along with four ICU fellows and six medical residents.

Subjects

All consecutive patients admitted to the medical ICU between February and April 2014 were included.

Data Collection

The following demographic and clinical data were collected from the patients: age, sex, underlying disease, reason for ICU admission, and route of ICU admission. The Acute Physiology and Chronic Health Evaluation (APACHE) II score was collected upon admission as the severity score. The perception of the intensivists toward ICU admission was categorized as non-beneficial admission, beneficial admission, or indeterminate state on the first day (day 1) and third day of ICU stay (day 3). The same physician who judged on day 1 was asked to judge the same patient's condition once again on day 3, considering the treatment response within 48–72 hours after ICU admission. The intensivists were also asked regarding the anticipated duration of survival of each patient who was perceived as non-beneficially admitted.

Non-beneficial Admission, Beneficial Admission, and Indeterminate State

When the four critical care specialists who participated in the study wanted to make a judgment of non-beneficial admission, they were asked to make a judgment based on the following three circumstances and to select one of them as the reason for their perception: (1) serious underlying disease and irreversibility; (2) serious neurologic condition; and (3) imminent death within 7 days, which were defined as follows. First, "serious underlying disease and irreversibility" refers to end-stage disease with no further treatment available. For example, the "serious underlying disease" is stage IV lung cancer, and "irreversibility" refers to a condition in which there are no more drugs to use to improve lung cancer or a patient is no longer in a condition to be treated for a disease. Second, a "serious neurologic condition" is a condition judged to have difficulties in achieving recovery of meaningful consciousness

in the future owing to serious neurological damage, such as severe brain injury. Third, "imminent death within 7 days" is defined as a condition in which death is predicted within a week because the current condition is very severe, and resuscitation is difficult even if intensive care is received. Beneficial admission was defined when the following three criteria were met: (1) a case that does not belong to any of the three abovementioned non-beneficial states, (2) when it is not expected that the patient would be dependent on life-sustaining treatment, and (3) when the patient is expected to recover after receiving intensive care and discharge from the ICU or the hospital. Meanwhile, when the patient's overall status remains at the boundary between non-beneficial and beneficial admissions, and it is difficult to determine either state, it was defined as "indeterminate" when the decision was withheld. The questionnaire used is provided as a Supplementary Material 1.

Main Outcomes and Definitions

The primary outcome was the ICU mortality rate. The secondary outcomes were the in-hospital and 6-month mortality rates and quality of life of the survivors 6 months after ICU discharge. The quality of life included the sensory-cognitive ability, physical activity, and degree of mobility. The level of sensory-cognitive ability was defined on the basis of the following four scores: 1, no ability; 2, severely limited; 3, mildly limited; and 4, no limitation. The level of physical activity was defined as follows: 1, bedridden; 2, able to sit; 3, able to occasionally ambulate; and 4, able to often ambulate. The degree of mobility was defined as follows: 1, no mobility; 2, severely limited; 3, mildly limited; and 4, no limitation.

Statistical Analysis

Continuous variables are reported as medians (interquartile range [IQR], 25%–75%) or means (±standard deviations) and categorical variables as numbers (percentages). Statistical analysis was performed using IBM SPSS ver. 25.0 (IBM Corp., Armonk, NY, USA). To assess the differences among the groups, we compared the data using the t-test or Mann-Whitney test for continuous variables and the chi-square or Fisher's exact test for categorical variables. Analysis of variance was used to compare the continuous variables among the three groups. A univariate analysis was performed with each variable using binary logistic regression. A multivariate analysis was performed with a backward, stepwise, logistic regression model. Variables that yielded P-values <0.05 in the univariate analysis were included in the multivariate analysis.

RESULTS

Patient Characteristics

A total of 210 patients were enrolled in this study. Their mean age was 64±14 years, and 139 patients (66%) were men. One third of the patients (34%) had solid tumor malignancy or hematologic malignancy. Acute respiratory failure was the most common (52%) reason for ICU admission. The mean APACHE II score at ICU admission was 25±9. Transfer from the general ward was the most common route of ICU admission (58%). Most of the patients, except for two, had consented to all possible treatments before admission to the ICU (Table 1).

Perceptions of the Intensivists Regarding Patient Admission to the ICU on Day 1 and Day 3

On day 1, 22 patients (10%) were perceived as having non-beneficial admission; 166 (79%), beneficial admission; and 22 (10%), indeterminate state (Table 2). On day 3, 202 of the 210 patients remained in the ICU. The eight patients were discharged between day 1 and day 3; three died, while five showed improved conditions and were transferred to the general ward. On day 3, the intensivists perceived 23 (11%) of the 202 patients as having non-beneficial admission; 159 (79%), beneficial admission; and 21 (10%), indeterminate state. The most common reason for the perception of non-beneficial admission was serious and irreversible underlying disease. The original perceptions on day 1 for 90% of the patients were sustained on day 3. For 20 (10%) patients, the perceptions changed. The perceptions for six (3%) of these patients changed to the contrary perception between day 1 and day 3 (from non-beneficial to beneficial or vice versa). The characteristics of these patients and clinical courses during the 3 days are described in Supplementary Table 1.

Outcomes

Among the total of 210 patients, the ICU mortality rate was 30%, and the in-hospital and 6-month mortality rates were 44% and 57%, respectively (Figure 1). Among the 22 patients who were perceived as having non-beneficial admission on day 1, 13 (59%) died in the ICU. Their in-hospital mortality rate increased to 82%. In this group, there were no survivors at the 6-month follow-up. In the beneficial admission group, the ICU, in-hospital, and 6-month mortality rates were 23%, 34%, and 48%, respectively; in the indeterminate state group, the mortality rates were 59%, 82%, and 82%, respectively. Even according to the day 3 perceptions, the non-beneficial admission

Table 1. Baseline characteristics

Characteristics	All patients (n=210)	Non-beneficial admission (n=22)	Beneficial admission (n=166)	Indeterminate state (n=22)	P-value
Age (yr)	64±14	63±14	64±14	68±15	0.474
Male	139 (66)	15 (68)	112 (68)	12 (55)	0.474
Underlying disease					
DM	66 (31)	8 (36)	50 (30)	8 (36)	0.730
Hypertension	91 (43)	7 (32)	72 (43)	12 (55)	0.314
Hepatitis	20 (10)	0	16 (11)	1 (5)	0.201
Pulmonary tuberculosis	32 (15)	3 (14)	24 (15)	5 (23)	0.570
Malignancy	71 (34)	11 (50)	54 (33)	6 (27)	0.210
Hematologic	24 (11)	4 (18)	19 (11)	1 (5)	0.350
Solid tumor	47 (22)	7 (32)	35 (21)	5 (23)	0.457
Liver cirrhosis	17 (8)	3 (14)	12 (7)	2 (9)	0.526
COPD	14 (7)	0	13 (8)	1 (5)	0.602
ESRD	9 (4)	1 (5)	6 (4)	2 (9)	0.285
Others	2 (1)	0	1 (1)	1 (5)	0.376
Reason for ICU admission					
Acute respiratory failure	109 (52)	10 (46)	83 (50)	16 (73)	0.109
Sepsis/septic shock	38 (18)	4 (18)	32 (20)	2 (9)	0.615
Postoperative care	16 (8)	0	16 (10)	0	0.119
Acute liver failure	13 (6)	1 (5)	10 (6)	2 (9)	0.866
Hemorrhagic shock	11 (5)	2 (9)	9 (5)	0	0.448
Heart failure/ACS	5 (2)	0	4 (2)	1 (5)	0.695
Acute renal failure	5 (2)	0	4 (2)	1 (5)	0.695
CPCR survivor	5 (2)	4 (18)	1 (1)	0	0.001
For procedure	4 (2)	0	4 (2)	0	1.000
Acute cerebral hemorrhage/stroke	2 (1)	1 (5)	1 (1)	0	0.376
For surgery	1 (1)	0	1 (1)	0	0.119
Others	1 (1)	0	1 (1)	0	1.000
APACHE II score at ICU admission	25±9	30±8	26±9	29±7	<0.001[a]
Route of ICU admission					
General ward	122 (58)	12 (55)	97 (58)	13 (59)	0.968
Emergency room	79 (38)	10 (25)	62 (37)	7 (32)	0.639
Transfer from other hospital	9 (4)	0	7 (4)	2 (9)	0.437
DNR status					
Before ICU admission	2 (1)	0	1 (1)	1 (1)	0.179
During ICU stay	61 (29)	12 (55)	35 (21)	14 (64)	<0.001
During the entire hospitalization	74 (35)	12 (55)	47 (28)	15 (68)	<0.001

Values are presented as mean±standard deviation or number (%).
DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease; ESRD: end-stage renal disease; ICU: intensive care unit; ACS: acute coronary syndrome; CPCR: cardiopulmonary cerebral resuscitation; APACHE: Acute Physiology and Chronic Health Evaluation; DNR: do-not-resuscitate.
[a]Non-beneficial admission group versus beneficial admission group, P=0.001; beneficial admission group versus indeterminate state group, P=0.011; non-beneficial admission group versus indeterminate state group, P=0.534.

group and the indeterminate state group showed high ICU, in-hospital, and 6-month mortality rates.

Expected and Actual Survival Times of the Patients Perceived as Having Non-beneficial Admission

The anticipated survival time of the non-beneficial admission

group was <4 weeks for 73% of the patients and 4 weeks to 6 months for 27% of the patients. The actual survival time was only 12 days (IQR, 4–53 days). For 46% of the patients, the anticipations of the intensivists were correct with regard to the actual survival time. In cases with discrepancy, the actual survival time was longer than the anticipated survival time. The differences between the two survival times were mostly within 1 week to 1 month (Supplementary Table 2).

Quality of Life 6 Months after ICU Discharge of the 6-Month Survivors

When the quality of life of the 6-month survivors after discharge from the ICU was compared with that at the time of admission to the ICU, the sensory-cognitive ability, physical

Table 2. Perception of the intensivists on patient admission to the ICU on day 1 and day 3

Characteristics	Day 1	Day 3
Perception of the intensivists	(n=210)	(n=202[a])
Non-beneficial admission	22 (10)	22 (11)
Beneficial admission	166 (79)	159 (79)
Indeterminate state	22 (10)	21 (10)
Reason for perception as non-beneficial admission	(n=22)	(n=22)
Serious underlying disease and irreversibility	18 (82)	19 (86)
Serious neurologic condition	2 (9)	3 (14)
Imminent death within 7 days	2 (9)	0

Values are presented as number (%).
ICU: intensive care unit.
[a]On day 3, 202 of the 210 patients remained in the ICU.

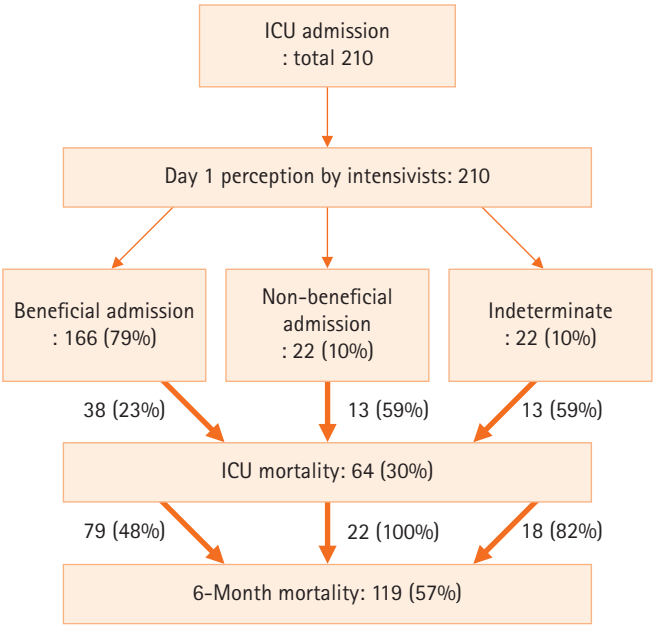

Figure 1. Outcomes of patients according to the perception of intensivists on the appropriateness of intensive care unit (ICU) admission. Among the patients who were perceived as having non-beneficial admission by intensivists or for whom it was difficult for the intensivists to decide whether their ICU admission was beneficial (indeterminate) on ICU day 1, more than half died in the ICU, while most of them died after 6 months.

Table 3. Quality of life 6 months after ICU discharge of the 6-month survivors

Variable for quality of life	ICU admission (n=91)	6 Months after ICU discharge (n=87)[a]	Interval improvement[a]
Sensory/cognitive ability			37 (43)
No ability	3 (3)	0	
Severely limited	24 (26)	5 (6)	
Mildly limited	22 (24)	9 (10)	
No limitation	42 (46)	73 (84)	
Physical activity			75 (86)
Bedridden	53 (58)	4 (4)	
Able to sit up	34 (37)	22 (24)	
Able to occasionally ambulate	2 (2)	23 (25)	
Able to often ambulate	2 (2)	38 (42)	
Degree of mobility			61 (70)
No mobility	10 (11)	2 (2)	
Severely limited	47 (52)	12 (13)	
Mildly limited	27 (30)	30 (33)	
No limitation	7 (8)	43 (47)	

Values are presented as number (%).
ICU: intensive care unit.
[a]Four patients missing.

activity, and degree of mobility showed a tendency to improve in most patients. In particular, the physical activity and degree of mobility showed significant improvements in the meantime in 86% and 70% of the patients, respectively (Table 3). Notably, 46% of the 6-month survivors had no impairment in the sensory/cognitive ability at the time of admission to the ICU; 84% of the patients had no disability at all 6 months after discharge.

Perceptions of the Intensivists as a Predictor for ICU and 6-Month Mortalities

To evaluate the predictors of survival from ICU and 6-month mortalities for all patients admitted to the ICU, we performed univariate and multivariate analyses. The comparisons of the characteristics of the survivors and non-survivors in each group are presented in Table 4. In the multivariate analysis, the day 3 perception of the intensivists as non-beneficial admission or indeterminate state (odds ratio [OR], 4.049; 95% confidence interval [CI], 1.892–8.664; P<0.001) and APACHE II score at ICU admission (OR, 1.074; 95% CI, 1.031–1.118; P<0.001) were found to be the significant predictive factors of ICU mortality (Table 5). Meanwhile, the day 1 perception of the intensivists as non-beneficial admission or indeterminate state (OR, 4.983; 95% CI, 1.260–19.703; P=0.022), day 3 perception of the intensivists as non-beneficial admission or indeterminate state (OR, 4.459; 95% CI, 1.162–17.121; P=0.029), solid tumor malignancy (OR, 3.411; 95% CI, 1.480–7.861; P=0.004), and male sex (OR, 2.616; 95% CI, 1.289–5.311; P=0.008) (Table 5) were found to be the significant predictive factors of 6-month mortality.

DISCUSSION

This study found that the perceptions of the intensivists toward the appropriateness of ICU admission were consistent with the prognosis of the critically ill patients. Thus, the perception of the intensivists was found as a significant predictor of not only ICU outcomes (short-term prognosis) but also 6-month outcomes (long-term prognosis).

In this series of patients, 10% of the ICU admissions were perceived as non-beneficial, 80% as beneficial, and 10% as indeterminate. The survival rate at the time of ICU discharge between the non-beneficial and beneficial admission groups was significantly different (36% vs. 78%), which further diverged at the 6-month follow-up (0% vs. 52%). Thus, the outcomes of the patients perceived as having non-beneficial admission were extremely poor. The main characteristics of this group of patients were a high APACHE II score, a high rate of malignancy, and a significantly higher proportion of cardiopulmonary cerebral resuscitation survivors than those of other groups. The ICU and 6-month survival rates of the patients who were perceived as having an indeterminate state were quite similar to those of the patients who were perceived as having non-beneficial admission. They showed similar characteristics to those of the beneficial admission group in terms of the distribution of comorbidities and to those of the non-beneficial admission group in terms of the initial severity. Meanwhile, most (96%) of the 6-month survivors included those whom the intensivists perceived as having beneficial admission on day 1. The quality of life of the 6-month survivors significantly improved over time, compared with that at ICU admission.

This study is unique from previous studies [1,3,10,11] in that the perceptions of the critical care physicians were evaluated on the first day of ICU admission and at another time point (day 3) after the very critical resuscitation period in the ICU. Interestingly, 9 out of 10 patients were classified under the same perception on day 3 as on day 1. A few non-beneficial admission perceptions on day 1 were changed to beneficial admission perceptions on day 3 when there was a significant change in the treatment plan or considerable improvement of acute disease. Meanwhile, a few beneficial admission perceptions were changed to non-beneficial admission perceptions when there was a progressive physiologic deterioration, such as the development of multi-organ failure. This switch in perception in our study was in agreement with that in a previous study that showed that the deterioration of acute physiologic state on the third day helped identify non-beneficial care better than that on the first day [12].

Critical care physicians often encounter patients of the indeterminate state group. Thus, it justifies the need for a trial of therapy [6,12]. In our study, the overall outcomes of the indeterminate state group were as poor as those of the non-beneficial admission group. Those perceived as having an indeterminate state on day 1 but a non-beneficial or beneficial admission on day 3 showed outcomes in agreement with the day 3 perceptions. However, those perceived as having beneficial or non-beneficial admission on day 1 but an indeterminate state on day 3 showed outcomes similar to the corresponding original outcomes on day 1. These findings suggest that critically ill patients with indeterminate prospects at the outset of ICU treatment may warrant therapeutic trial of 3 days to determine the short-term and long-term prognoses with better accuracy. In cases where physicians cannot still make a judgment after the therapeutic trial, the chances for

Table 4. Comparison of the characteristics of the patients according to ICU and 6-month mortalities

Characteristics	ICU outcome			P-value	6-month outcome		P-value
	All patients (n=210)	Survivor (n=146)	Non-survivor (n=64)		Survivor (n=91)	Non-survivor (n=119)	
Age (yr)	64±14	64±15	66±13	0.31	64±16	65±13	0.809
Male	139 (66)	96 (66)	43 (67)	0.84	52 (57)	87 (73)	0.015
Underlying disease							
DM	66 (31)	45 (31)	21 (33)	0.775	31 (34)	35 (29)	0.155
Hypertension	91 (43)	66 (45)	25 (39)	0.408	41 (45)	50 (42)	0.660
Hepatitis	20 (10)	11 (8)	9 (14)	0.138	7 (8)	13 (11)	0.429
Pulmonary tuberculosis	32 (15)	19 (13)	13 (20)	0.176	10 (11)	22 (19)	0.134
Malignancy	71 (34)	49 (34)	22 (34)	0.909	18 (20)	53 (45)	<0.001
Hematologic	24 (11)	15 (10)	9 (14)	0.427	7 (8)	17 (14)	0.137
Solid tumor	47 (22)	34 (23)	13 (20)	0.634	11 (12)	36 (30)	0.002
Liver cirrhosis	17 (8)	10 (7)	7 (11)	0.317	3 (3)	14 (12)	0.026
COPD	14 (7)	12 (8)	2 (3)	0.236	9 (10)	5 (4)	0.102
ESRD	9 (4)	7 (5)	2 (3)	0.725	7 (8)	2 (2)	0.042
Others	2 (1)	1 (1)	1 (2)	0.518	0	2 (2)	0.507
Reason for ICU admission							
Acute respiratory failure	109 (52)	75 (51)	34 (53)	0.815	50 (55)	59 (50)	0.441
Sepsis/septic shock	38 (18)	29 (20)	9 (14)	0.315	16 (18)	22 (19)	0.866
Postoperative care	16 (8)	16 (11)	0	0.003	10 (11)	6 (5)	0.107
Acute liver failure	13 (6)	8 (6)	5 (8)	0.541	5 (6)	8 (7)	0.714
Hemorrhagic shock	11 (5)	7 (5)	4 (6)	0.739	4 (4)	7 (6)	0.760
Heart failure/ACS	5 (2)	1 (1)	4 (6)	0.031	0	5 (4)	0.071
Acute renal failure	5 (2)	3 (2)	2 (3)	0.642	3 (3)	2 (2)	0.654
CPCR survivor	5 (2)	1 (1)	4 (6)	0.031	0 (0)	5 (4)	0.071
For procedure	5 (2)	4 (3)	1 (2)	1.000	2 (2)	3 (3)	1.000
Acute CVA	2 (1)	1 (1)	1 (2)	0.518	0	2 (2)	0.507
For surgery	16 (8)	16 (11)	0	0.003	10 (11)	6 (5)	0.290
Others	1 (1)	1 (1)	0	1.000	1 (1)	0	0.433
APACHE II score at ICU admission	25±9	23±8	29±9	<0.001	23±9	26±9	0.027
Route of ICU admission							
GW	122 (58)	83 (57)	39 (61)	0.580	47 (52)	75 (63)	0.098
ER	79 (38)	55 (38)	24 (38)	0.981	40 (44)	39 (33)	0.097
Transfer from other hospital	9 (4)	8 (6)	1 (2)	0.282	4 (4)	5 (4)	1.000
Day 1 perception of the intensivists							
Non-beneficial admission or indeterminate state	44 (21)	18 (12)	26 (41)	<0.001	4 (4)	40 (34)	<0.001
Day 3 perception of the intensivists							
Non-beneficial admission or indeterminate state	43 (20)	17 (12)	26 (41)	<0.001	4 (4)	39 (33)	<0.001

Values are presented as mean±standard deviation or number (%).
ICU: intensive care unit; DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease; ESRD: end-stage renal disease; ACS: acute coronary syndrome; CPCR: cardiopulmonary cerebral resuscitation; CVA: cerebrovascular accident (hemorrhage or stroke); APACHE II: Acute Physiology and Chronic Health Evaluation II; GW: general ward; ER: emergency room.

meaningful outcomes are thought to be poor, as in those of the non-beneficial admission group on day 1.

The intensivists in our study were asked to provide an estimate of the anticipated survival time of the non-beneficial admission group. They expected those patients to survive for as long as 1 to 6 months. However, no intensivist expected a

Table 5. Predictive factors for ICU and 6-month mortalities among the patients admitted to the ICU

Variable	ICU mortality				6-Month mortality			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Male					2.309 (1.141–3.642)	0.016	2.616 (1.289–5.311)	0.008
Underlying disease								
Malignant solid tumor					3.154 (1.502–6.623)	0.002	3.411 (1.480–7.861)	0.004
Liver cirrhosis					3.911 (1.089–14.049)	0.037	3.855 (0.976–15.226)	0.054
Reason for ICU admission								
Heart failure/ACS	9.667 (1.058–88.283)	0.044	8.597 (0.818–90.333)	0.073				
CPCR survivor	9.667 (1.058–88.283)	0.044						
APACHE II score at ICU admission	1.094 (1.052–1.137)	<0.001	1.074 (1.031–1.118)	<0.001	1.037 (1.004–1.071)	0.029		
Day 1 perception of the intensivists								
Non-beneficial admission or indeterminate state	4.865 (2.412–9.814)	<0.001			11.013 (3.77–32.17)	<0.001	4.983 (1.260–19.703)	0.022
Day 3 perception of the intensivists								
Non-beneficial admission or indeterminate state	5.418 (2.645–11.101)	<0.001	4.049 (1.892–8.664)	<0.001	11.486 (3.919–33.663)	<0.001	4.459 (1.162–17.121)	0.029

All patients: n=210.
ICU: intensive care unit; OR: odds ratio; CI: confidence interval; ACS: acute coronary syndrome; CPCR: cardiopulmonary cerebral resuscitation; APACHE: Acute Physiology and Chronic Health Evaluation.

survival time of over 6 months. This consequently suggests that intensivists, at least in our study, perceive that beneficial admission should ensure at least a 6-month survival. In this regard, the current statement regarding the appropriate goal of ICU care [8], defining appropriateness simply as survival outside acute care settings, may not be precise enough for individual situations. It also indicates that the perceptions of intensivists toward the appropriateness of ICU admission are more consistent with the long-term prognosis than with the immediate outcomes of ICU admission. Recent studies have also confirmed that ICU physicians predict a patient's prognosis with a longer view [13].

The current scoring system for critically ill patients provides information on the short-term mortality rate but has limitations in predicting the patient's condition in terms of long-term prognosis and quality of life issues [14-16]. This is where the role of critical care physicians arise. In this study, when the intensivists judged the futility of ICU admission based on their expertise, their perceptions were found to be in good agreement with not only the short-term but also the long-term prognosis. These results suggest the possibility that intensivists' perceptions can supplement the limitations of the current scoring system. In other words, the patient's prognosis should not be viewed solely based on physiological values, such as the APACHE II score; instead, the intensivist's perception on futility should be considered as important. This is because most ICU physicians inform the family regarding the patient's prognosis largely based on their professional perception and experience rather than applying a specific scoring system. The implications of our study are also consistent with existing views [17]. Meanwhile, considering an example in which human perception can serve as an objective indicator, such as the intensivist's perception, when evaluating dyspnea, the patient's subjective perception is used as an objective tool, including the New York Heart Association functional classification [18] and Medical Research Council dyspnea scale [19,20]. Further, just as the perception of pain is used as a tool for pain scales [21], the perception of intensivists can also be accepted as an important indicator for evaluating the prognosis of patients.

This study has several limitations. First, the study was performed at the medical ICU of a single center, which precludes the generalization of the findings. In particular, the number of patients perceived as having non-beneficial admission was too small to draw a firm conclusion on their characteristics. Second, because the intensivists participating in the study have been practicing for more than 10 years, the perceptions of in-

tensivists of less expertise and the resultant findings may differ from those of our study. In this context, since one patient was judged by only one physician, how consistent the perceptions for the patient among the intensivists were not investigated. Finally, the blinding method was not applied in this study, and the study participants judged and participated in the actual treatment decision. Therefore, the possibility of affecting the patient's prognosis cannot be excluded, though we attempted to minimize the impact by providing intensive care for the first 3 days with all possibilities open.

In conclusion, this study indicates that the intensivist's perception toward the appropriateness of ICU admission is quite consistent with the actual prognosis of the patient, especially the long-term prognosis. The findings suggest that the intensivist's perception on medical futility can compensate the limitations of the current scoring system for critically ill patients and therefore be an important tool in creating a new prognostic model that can predict patients' long-term outcomes. The role of critical care physicians can be reflected in the utilization of limited ICU resources.

CONFLICT OF INTEREST

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

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Conceptualization: CML. Data curation: YC, KRK. Formal analysis: YC. Methodology: CML, YC. Project administration: CML, YC, KRK. Visualization: CML, YC. Writing–original draft: CML, YC. Writing–review & editing: YC, CML, YK, JWH, SBH.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4266/acc.2021.00283.

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Supplementary Material 1. Questionnaire on the perception of intensivists on the appropriateness of intensive care unit admission

Term Definitions

1) Non-beneficial admission is defined when one of the following three conditions is satisfied: (1) serious underlying disease and irreversibility; (2) serious neurologic condition; and (3) imminent death within 7 days, which are defined as follows. First, "serious underlying disease and irreversibility" refers to end-stage disease with no further treatment available. For example, the "serious underlying disease" is stage IV lung cancer, and "irreversibility" refers to a condition in which there are no more drugs to use to improve lung cancer or a patient is no longer in a condition to be treated for a disease. Second, a "serious neurologic condition" is a condition evaluated to have difficulties in achieving recovery of meaningful consciousness in the future owing to serious neurological damage, such as severe brain injury. Third, "imminent death within 7 days" is defined as a condition in which death is predicted within a week because the current condition is very severe, and resuscitation is difficult even if intensive care is received.
2) Beneficial admission is defined when one of the following three conditions is satisfied: (1) a case that does not belong to any of the three abovementioned non-beneficial states, (2) when it is not expected that the patient would be dependent on life-sustaining treatment, and (3) when the patient is expected to recover after receiving intensive care and discharge from the intensive care unit (ICU) or the hospital.
3) Indeterminate state is defined when the decision is withheld when a patient's overall status remains at the boundary between non-beneficial and beneficial admissions and it is difficult to determine either state.

I. Day 1 (ICU admission)

Question 1) According to the abovementioned definitions, do you think this patient's ICU admission will be beneficial or non-beneficial? If it is difficult to decide based on the current state alone, please select indeterminate.

1) Non-beneficial
2) Beneficial
3) Indeterminate

Question 2) If you perceived it as non-beneficial, why did you judge it that way?

1) Serious underlying disease and its irreversibility
2) Serious neurologic condition
3) Imminent death within 7 days

II. Day 3 (48–72 hours after ICU admission)

Question 1) According to the abovementioned definitions, do you think this patient's ICU admission will be beneficial or non-beneficial? If it is difficult to decide based on the current state alone, please select indeterminate.

1) Non-beneficial
2) Beneficial
3) Indeterminate

Question 2) If you perceived it as non-beneficial, why did you judge it that way?

1) Serious underlying disease and its irreversibility
2) Serious neurologic condition
3) Imminent death within 7 days

Supplementary Table 1. Demographics and clinical courses of the patients with changes in perception between day 1 and day 3

Day 1	Day 3	No.	Sex/age (yr)	Underlying disease	Reason for ICU admission	ICU course between day 1 and day 3
Non-beneficial admission	Beneficial admission	1	M/58	Amyopathic dermatomyositis-related organizing pneumonia Bronchiectasis	Acute respiratory failure d/t pneumonia with RV failure Septic shock d/t perianal abscess	Venous-arterial ECMO d/t deteriorated RV failure → considering lung transplantation
		2	M/73	AML with persistent disease state after study chemotherapy		Clinically improving state with reduced dose of vasopressor
Beneficial admission	Non-beneficial admission	1	M/75	Esophageal cancer (surgery refused) s/p induction chemotherapy s/p definite concurrent chemo-radiation therapy 3 months ago → stable disease with ECOG PS 3 pneumonia twice within the recent 2 months	Acute respiratory failure d/t asphyxia with GI bleeding	Increased oxygen requirement with severe muscle weakness
		2	M/57	Neuroendocrine tumor with tracheal invasion, cardiac, liver metastasis with SVC syndrome	For procedure (tracheal stent insertion with ECMO therapy)	Successful procedure and weaning off ECMO but with progressive tumor lysis syndrome and multi-organ failure
		3	M/73	AML, M0 s/p 2nd chemotherapy 5 days ago ECOG PS 0 COPD Hypertension Gout	Acute respiratory failure with septic shock d/t aspiration pneumonia with colitis during chemotherapy	Progressive septic shock Severe hypoxemia Severe intra-abdominal hypertension Multi-organ failure
		4	M/80	COPD Atrial fibrillation Hypertension History of pulmonary tuberculosis History of CABG at 10 years ago	Acute respiratory failure d/t pneumonia with COPD aggravation	Deteriorated lung compliance Suspected obstructive pneumonitis d/t lung cancer (higher possibility of the presence of lung cancer)

ICU: intensive care unit; RV: right ventricle; ECMO: extracorporeal membrane oxygenation; AML: acute myeloid leukemia; ECOG PS: Eastern Cooperative Oncology Group performance status; GI: gastrointestinal; SVC: superior vena cava; COPD: chronic obstructive disease; CABG: coronary artery bypass graft.

Supplementary Table 2. Expected and actual survival times of the patients perceived as having non-beneficial admission

Characteristics	Intensivists (n=22)
Expected survival time on ICU admission	n (%)
<1 week	5 (23)
1–2 weeks	4 (18)
3–4 weeks	7 (32)
1–6 months	6 (27)
>6 months	0
Actual survival time on ICU admission (day)	12 (4–53)
Consistency between the expected and actual survival times	10 (46)
If discordant,	12 (54)
Expected less	8 (67)
Expected more	4 (33)
Difference between the expected and actual survival times	
Within 1 week	1 (8)
Between 1 week and 1 month	9 (75)
Between 1 month and 3 months	2 (17)
Between 3 months and 6 months	0
Between 6 months and 1 year	0
More than 1 year	0

Values are presented as number (%) or median (interquartile range).
ICU: intensive care unit.

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Associations between systemic inflammation and intestinal permeability with Onodera's prognostic nutritional index in critically ill patients

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Background: Malnutrition is a serious condition in critically ill patients. The aim of this study is to evaluate the relationships between the Onodera's prognostic nutritional index (OPNI) and intestinal permeability and between OPNI and systemic inflammation in critically ill patients.

Methods: This was a cross-sectional study conducted in the general intensive care unit (ICU) of a university-affiliated hospital. A total of 162 patients admitted between May 2018 and December 2019, was included in the study. The OPNI was calculated at admission and categorized as ≤40 or >40. We assessed plasma endotoxin and zonulin concentrations as markers of intestinal permeability as well as serum interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hs-CRP) as markers of systemic inflammation upon admission under stringent conditions. The relationships between these markers and OPNI were assessed after adjusting for potential confounders through estimation of a binary logistic regression model.

Results: Median (interquartile range) hs-CRP, IL-6 zonulin, and endotoxin were significantly greater in the low OPNI subgroup than in the high OPNI subgroup (all P<0.05). Multivariate analyses showed significant association between serum IL-6 (odds ratio [OR], 0.88; 95% confidence interval [CI], 0.64–0.96), serum hs-CRP (OR, 0.77; 95% CI, 0.53–0.92), plasma endotoxin (OR, 0.81; 95% CI, 0.72– 0.93), and plasma zonulin (OR, 0.83; 95% CI, 0.75–0.98) levels with OPNI in the overall population.

Conclusions: Our results provide evidence that higher plasma endotoxin, zonulin, IL-6, and hs-CRP levels are associated with progressively lower OPNI in mixed ICU populations, particularly in surgical ICU patients.

Key Words: C-reactive protein; endotoxin; intensive care unit; interleukin-6; zonulin; Onodera

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INTRODUCTION

Malnutrition is a common unfavorable complication in critically ill patients [1]. According to previous studies, about two-thirds of patients admitted to intensive care units (ICUs) are malnourished [2]. Inadequate nutritional delivery can result in increased morbidity and mortality in malnourished ICU patients [3,4].

Delaying initiation of nutrition support can significantly increase inflammation and impair intestinal barrier function, which can lead to intestinal atrophy and bacterial translocation [5]. Critically ill patients with pre-existing systemic inflammatory state experience severe catabolic stress [6]. An inflammatory response is induced following injury to maintain homeostasis [7]. Widespread inflammation in systemic inflammatory response syndrome is usually present in areas remote from the site of initial injury [7]. Bacterial translocation is commonly associated with septic complications [8]. It has been proposed that bacterial translocation and the presence of systemic inflammation are involved in the pathogenesis of systemic infectious complications and multiple organ deficiency syndromes [8].

Nutrition assessment in critically ill patients is crucial for classifying nutritional status, identifying nutritional problems, and monitoring nutritional support adequacy [9]. Most importantly, establishing early nutrition-related prognoses in patients is pivotal to oversee nutritional progress and distinguish patients at risk of complications and who would benefit from particular nutrition interventions [9,10]. An ideal nutrition index is calculated to accurately evaluate nutritional status in critically ill patients. In clinical practice, the Onodera's prognostic nutritional index (OPNI) is widely used as a simple and cost-effective index to evaluate patient nutritional status [11]. It was initially developed by Onodera et al. [11] to predict the risk of postoperative complications after gastrointestinal surgery. OPNI has been shown to predict prognosis in different types of cancer [12-15]. It is simple formula to assess total lymphocyte count and serum albumin [11], with lower OPNI scores associated with poorer outcomes [16,17]. As one of the simplest and most commonly used measures, it is a valuable nutritional index to evaluate the nutritional status of critically ill patients.

There is much debate regarding whether associations exist between nutritional status and inflammation and nutritional status and intestinal permeability in critically ill patients. We hypothesized that critically ill patients with low OPNI have increased intestinal permeability and systemic inflammation, as well as worse clinical outcomes. However, our current knowledge for critically ill patients is rudimentary. Thus, the current study has two main objectives. The first is to assess the relationships between levels inflammatory and intestinal permeability factors at admission with OPNI score in critically ill patients. The second is to identify possible associations of clinical outcomes with OPNI.

KEY MESSAGES

- Elevated plasma levels of zonulin and endotoxin are related with lower Onodera's prognostic nutritional index (OPNI), particularly in surgical intensive care unit patients.
- Higher serum interleukin-6 and high-sensitivity C-reactive protein levels are associated with lower OPNI.

MATERIALS AND METHODS

Study Design and Participants

We conducted a cross-sectional study between May 1, 2018, and December 31, 2019, in the mixed ICU of a university-affiliated hospital. Inclusion criteria were age 18 and above and admitted to the ICU. Patients were excluded if they were discharged within 24 hours of ICU admission or died and if they were transferred from other ICUs. A total of 162 patients was enrolled within 24 hours of ICU admission. All clinical and demographic data were collected from the first admission for those who were readmitted to the ICU. Reasons for hospitalization were classified as either medical or surgical.

Baseline Characteristics and Clinical Measurements

Baseline demographic information, laboratory data, and past medical history including detailed lists of laboratory values and comorbidities were collected by investigators blinded to clinical outcomes. Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores [18,19] were recorded within the first 24 hours of admission to ICU. Venous blood was collected in ethylenediaminetetraacetic acid-containing tubes from an antecubital vein during the morning of the first day of admission in the ICU. Plasma was separated by centrifugation at 3,000 rpm for 10 minutes at 4°C within 30 minutes of collection. Then, both plasma and serum samples were snap-frozen and stored in small aliquots at – 80°C to prevent repeated freezing and thawing until measurement of laboratory data. A commercially available human interleukin-6 (IL-6) enzyme-linked immunosorbent assay (ELISA) kit (Bender Medsystems, Burlingame, CA, USA) was used to measure serum IL-6. Plasma zonulin level was analyzed by ELISA (Immundiagnostik, Bensheim, Germany), and plasma endotoxin levels were measured by a commercially available quantitative chromogenic endpoint *Limulus* amoebocyte lysate QCL-1000 kit (Lonza, Walkersville, MD, USA). In addition, an ELISA kit was used to estimate

high-sensitivity C-reactive protein (hs-CRP) (Diagnostics Biochem, London, ON, Canada). All laboratory tests were performed using the same blood sample for each patient. All tests were carried out in duplicate, and all assays were utilized as recommended by the manufacturers.

The OPNI for each patient was calculated using the formula: OPNI=10×albumin (g/dl)+0.005×total lymphocyte count/μL as measured in peripheral blood, with a reference value ≤40 [11]. Serum albumin and lymphocyte count were measured within 24 hours of admission to the ICU. Clinical outcomes, including incidence of sepsis according to American College of Chest Physicians and the Society of Critical Care Medicine criteria [20] during the ICU stay, mortality in the ICU, and length of stay in the ICU were recorded.

Ethical Statement

The study was supported by grant NO 1395/74351 from the Shahid Beheshti University of Medical Sciences. All procedures performed in studies involving human participants were in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from the legal representatives of eligible patients according to local regulations. This study was reviewed and approved by the ethics committee of Shahid Beheshti University of Medical Sciences with Ethical approval (No. IR.SBMU.RETECH.REC.1395.860).

Statistical Analysis

All statistical analyses were carried out using IBM SPSS ver. 20 (IBM Corp., Armonk, NY, USA). The significance level of all tests was targeted at 0.05. Characteristics of the study population were analyzed by descriptive statistics. Data were expressed as percentages and frequencies or described as medians and interquartile range (IQR) for continuous variables not normally distributed and highly skewed. Using OPNI as the categorical variable, patients were placed into two categories: high OPNI (>40) and low OPNI (≤40). The differences in distributions of categorical variables were assessed using chi-square test, whereas the Mann-Whitney test was used to assess differences in the distributions of continuous variables. Univariate binary logistic regression was used to explore relationships between OPNI and intestinal permeability (zonulin and endotoxin levels) or inflammatory factors (hs-CRP, IL-6) for the overall population and by admission category. Multiple logistic regression models were adjusted for age and used to determine relationships between exploratory variables and OPNI with adjustment for potential confounders. Initially, a partially adjusted model included age. A fully adjusted model added APACHE II. Variance inflation factor was used to detect collinearity in the final model.

RESULTS

The final analyses were conducted in a sample of 162 critically ill patients (Figure 1). Demographic and clinical characteristics of the 162 included patients are listed in Table 1, overall and by OPNI. The median age of participants was 65 years (IQR, 49–75), and 54% were male. Overall, 63% of patients were classified as low nutritional status according to OPNI.

Patients were dichotomized based on OPNI cut-off. The median age of patients with low or high OPNI was 69.5 years (IQR, 51–79 years) and 58 years (IQR, 49–70 years), respectively (P=0.002). There were no significant differences in APACHE II score and SOFA score between the two OPNI subgroups. (P=0.066 and P=0.519, respectively). At admission, there was a statistically significant difference between low and high OPNI subgroups (P=0.021). As expected, compared to patients with high OPNI, the low OPNI subgroup had significantly lower serum albumin (P<0.001) and lower lymphocyte count (P<0.001). The median (IQR) serum IL-6 of participants was 318 pg/ml (96–477 pg/ml) and 157 pg/ml (43–422 pg/ml) in low and high OPNI subgroups, respectively, demonstrating a significant difference (P<0.001). The median (IQR) serum hs-CRP was significantly greater in the low OPNI subgroup than in patients with high OPNI (P=0.006). Those with low OPNI exhibited significantly higher plasma zonulin and plasma endotoxin values

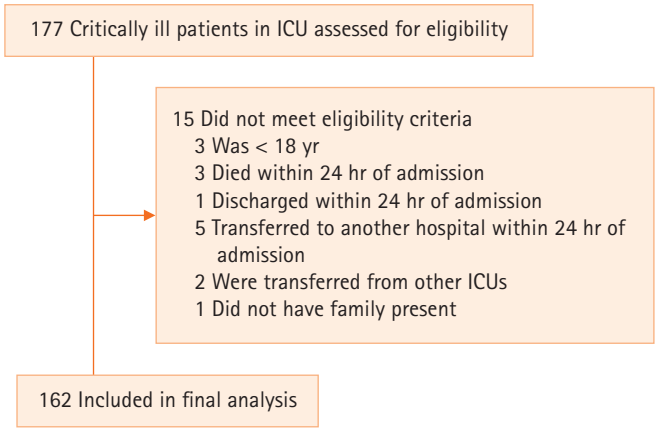

Figure 1. Flowchart describing selection of participants. ICU: intensive care unit.

Table 1. Baseline demographic and clinical characteristics of the overall population according to OPNI class

Variable	Overall (n=162)	OPNI class		
		Low (≤40, n=102)	High (>40, (n=60)	P-value
Age (yr)	65 (49–75)	69.5 (51–79)	58 (49–70)	0.002[a,b]
Sex				0.088[a,c]
Male	87 (53.7)	60 (59)	27 (45)	
Female	75 (46.3)	42 (41)	33 (55)	
Hospital to ICU admission (day)	0.5 (0–1)	0 (0–1)	1 (0–1)	0.242[b]
Admission category				0.021[a,c]
Medical	78 (48)	42 (41)	36 (60)	
Surgical	84 (52)	60 (59)	24 (40)	
Number of comorbidities	0 (0–2)	1 (0–2)	0 (0–1)	0.043[a,b]
Mechanical ventilation	34 (21)	20 (20)	14 (23)	0.574[c]
APACHE II score	26 (21–36)	25 (20–35)	28 (21–40)	0.066[b]
SOFA score	8 (7–11)	8 (7-11)	9 (6-11)	0.519[b]
OPNI score	32.2 (24.5–45.3)	27.5 (21.3–31.8)	46.9 (43.9–51.5)	<0.001[a,b]
Total lymphocyte count	1,513 (890–2,386)	1,163 (688–1,546)	2,533 (2,024–2,899)	<0.001[a,b]
Serum albumin (g/dl)	2.5 (2–3.4)	2 (1.7–2.4)	3.5 (3.3–3.9)	<0.001[a,b]
Serum IL-6 (pg/ml)	222 (77–454)	318 (96–477)	157 (43–422)	<0.001[a,b]
Serum hs-CRP	4.01 (2.98–4.52)	4.28 (3.77–4.60)	2.30 (1.56–3.58)	0.006[a,b]
Plasma zonulin (ng/ml)	6.8 (4.3–11.5)	8.2 (5.0–12.1)	6.0 (3.5–9.5)	0.022[a,b]
Plasma endotoxin (EU/mL)	0.57 (0.33–0.86)	0.66 (0.40–0.88)	0.48 (0.31–0.78)	0.034[a,b]

Values are presented as median (interquartile range) or number (%).
OPNI: Onodera's prognostic nutritional index; ICU: intensive care unit; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; IL-6: interleukin-6; hs-CRP: high-sensitivity C-reactive protein.
[a]P<0.05, statistically significant; [b]Mann-Whitney test; [c]Chi-square test.

compared with those with high OPNI (P<0.001 for both comparisons).

Multivariate analyses using binary logistic regression (OPNI classification: low or high) demonstrated significant relationship between higher plasma zonulin level and lower OPNI with adjusted odds ratio (OR) 0.83 (95% confidence interval [CI], 0.75–0.98) in the overall population, OR 0.81 (95% CI, 0.78–0.96) in the surgical group, and OR 0.91 (95% CI, 0.89–1.21) in the medical group (Table 2). A significant negative association between endotoxemia and decreasing OPNI category was demonstrated in the overall population (OR, 0.81; 95% CI, 0.72–0.93) and in the surgical group (OR, 0.79; 95% CI, 0.75–0.89) (Table 2).

In the first model, there was a significant negative association of IL-6 with OPNI category in the overall population and in both surgical and medical groups. However, the association remained significant only in the overall population (OR, 0.88; 95% CI, 0.64-0.96) and in the surgical group (OR, 0.80; 95% CI, 0.60–0.88) after adjustments for potential confounders (Table 2). An inverse correlation was found between hs-CRP level and OPNI category in the overall population and in both surgical and medical groups, which are demonstrated in the first and second models (Table 2).

There was statistically significant difference in the incidence of new severe sepsis between OPNI categories. Overall, 28.4% of those in the low OPNI group versus 13.3% in the high OPNI group had new severe sepsis (P=0.027). There were no statistically significant differences for mortality in ICU between the low OPNI group (18.6%) and the high OPNI group (13.3%) (P=0.027). The median (IQR) length of stay in ICU was 17 (10–29) days and 11 (6–24) days for the low OPNI group and the high OPNI group, respectively (P=0.042).

DISCUSSION

This study was conducted to assess the association of inflammation factors and intestinal permeability with nutritional status index (OPNI) in critically ill patient. Based on our literature review, potential associations of markers of intestinal permeability and inflammation with OPNI were not investigated in

Table 2. Binary logistic regression to predict the associations of intestinal permeability/inflammation factors with OPNI in the overall population and stratified by admission category

Variable	Overall (n=162)		Admission category			
			Medical (n=78)		Surgical (n=84)	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value[a]
Plasma zonulin						
First model	0.75 (0.69–0.89)	0.023	0.79 (0.75–0.98)	0.049	0.71 (0.60–0.80)	0.015
Second model[b]	0.83 (0.75–0.98)	0.048	0.91 (0.89–1.21)	0.114	0.81 (0.78–0.96)	0.044
Plasma endotoxin						
First model	0.73 (0.69–0.81)	0.021	0.80 (0.71–0.90)	0.032	0.73 (0.69–0.89)	0.032
Second model[b]	0.81 (0.72–0.93)	0.039	0.84 (0.80–1.09)	0.069	0.79 (0.75–0.89)	0.043
Serum IL-6						
First model	0.80 (0.70–0.90)	0.039	0.91 (0.88–1.11)	0.192	0.76 (0.75–0.80)	0.034
Second model[b]	0.88 (0.64–0.96)	0.042	0.92 (0.82–1.23)	0.236	0.80 (0.60–0.88)	0.038
Serum hs-CRP						
First model	0.74 (0.60–0.86)	0.031	0.78 (0.58–0.88)	0.040	0.65 (0.47–0.73)	0.012
Second model[b]	0.77 (0.53–0.92)	0.025	0.79 (0.59–0.98)	0.048	0.68 (0.52–0.77)	0.014

OPNI: Onodera's prognostic nutritional index; OR: odds ratio; CI: confidence interval.
[a]P<0.05; [b]Adjusted for age and Acute Physiology and Chronic Health Evaluation (APACHE) II score.

previous studies. Due to the wide range of diagnoses, patients enrolled in the study were divided into medical and surgical groups with a higher prevalence of surgical patients.

The results of our analysis demonstrate that higher plasma endotoxin, zonulin, IL-6, and hs-CRP levels are associated with progressively lower OPNI in medical-surgical ICU patients. These associations remained significant after adjusting for potential confounders (age and APACHE II). Moreover, our results indicated that this association was more identifiable in surgical ICU patients. These observations underscore the importance of nutritional condition in the recovery of systemic inflammation and intestinal barrier function [21]. The difference in the association of intestinal permeability and OPNI score between the surgical group and the medical group might be due to small sample size or might indicate that OPNI is a more appropriate indicator for assessing nutritional status in surgical patients. Therefore, we recommend that future studies with larger sample sizes be performed in both medical and surgical groups.

Studies have demonstrated that the OPNI predicts mortality, morbidity, and prognosis in several diseases including non-surgical conditions [11,22-25]. However, OPNI has rarely been applied in the ICU setting [26]. Similar to a previous study conducted by Vermeulen et al. [26], the mean OPNI in our study was lower than the reference value [11]. In our previous study of critically ill patients, we found a significant positive association between intestinal permeability markers and high scores for nutritional risk [27]. Consistent with our results, Kang et al. [24] reported that, in peritoneal dialysis patients, OPNI and serum albumin were negatively correlated with CRP. Furthermore, Yenibertiz et al. [15] showed that CRP was significantly higher in a low OPNI group of patients with small-cell lung cancer. Higher hs-CRP, lower OPNI, and older age are significant predictive factors for mortality among patients with total colectomy [28]. Milan Manani et al. [29] reported that IL-6 was negatively correlated with serum albumin in peritoneal dialysis patients. Decreased rate of albumin synthesis in critically ill patients results in hypoalbuminemia, which is often caused by combined effects of inflammation and malnutrition. Inflammation alone increases the fractional catabolic rate and alters the distribution of albumin between the intra- and extravascular compartments [30].

Two common complications seen in critically ill patients admitted to the ICU are increased systemic inflammation and intestinal permeability [7,8]. The leaky gut hypothesis explains that gut microbial products can cause chronic low-grade inflammation due to intestinal barrier dysfunction [31]. Infections or any trauma of the epithelial lining can severely damage intestinal barrier function, disrupting tissue homeostasis. Alteration of the gut barrier can lead to increased intestinal permeability, alter mucus composition and the intestinal layer, secretion of intestinal proteases, and damage to intestinal cells [32]. In addition, metabolic stress can induce secretion of pro-inflammatory cytokines and reactive oxygen species in

intestinal epithelium.

Proinflammatory responses occur simultaneously with anti-inflammatory responses to maintain immunological balance; this condition is called compensatory anti-inflammatory response syndrome. During this state, the immune systems of critically ill patients reprogram their defense strategies and are often unable to eliminate the primary infection, often resulting in secondary infection [32]. Nutrition in critically ill patients admitted to the ICU deteriorates rapidly regardless of nutritional status at the time of admission [33]. Severe catabolism and the proinflammatory state due to increase in both hormones and cytokines can result in rapid loss of protein. This phenomenon differentiates critically ill patients from other types of hospitalized patients among whom malnutrition is mostly related to decreased food intake due to the disease state. Thus, it is important to observe the current metabolic states of critically ill patients during nutrition assessment even when admitted in a well-nourished state [34].

Higher levels of systemic inflammation in the body, structure, and function of intact mucous membrane and leakage of toxins such as bacterial endotoxins are highly associated with malnutrition [21]. In addition, malnutrition reduces the ratio of CD4+ to CD8+ T cells as well as the appearance of peripheral immature T cells [35]. Low levels of lymphocyte types (CD19) indicate some nutritional deficiencies [36]. Therefore, the relationship between circulating lymphocyte counts and malnutrition has been shown to be crucial in identifying nutrient deficiencies.

The strengths of this study are the analysis of blood samples analyzed at a central laboratory and data collected by standardized procedures. The OPNI is a well-validated and simple tool that can be calculated using only two parameters and applied to a large number of patients in critical care settings. As for the limitations of this study, the highly heterogeneous group of patients poses interpretive challenges. Therefore, to confirm the results of this study, further investigations should focus on specific populations. Clinical status and the use of medications in critically ill patients can alter albumin level and total lymphocyte count and make them difficult to interpret. Therefore, these parameters were determined over the first 24 hours after admission at the ICU. Another limitation is that longitudinal associations of IL-6, hs-CRP, endotoxin, and zonulin levels with OPNI cannot be detected due to the cross-sectional study design. The possibility that residual confounding factors explain the associations of IL-6, hs-CRP, endotoxin, and zonulin levels with OPNI cannot be excluded. Another limitation of this study is that we did not calculate sample size based on the medical and surgical groups. Further investigation involving a more accurate lymphocyte count or subset is necessary.

In conclusion, higher plasma endotoxin, zonulin, IL-6, and hs-CRP levels are significantly negatively associated with OPNI in a mixed ICU population, particularly in surgical ICU patients. According to our findings, screening critically ill patients using the OPNI that can indicate systemic inflammation and intestinal permeability was suggested. Patients with lower OPNI benefit more from nutritional interventions compared to those with higher OPNI.

CONFLICT OF INTEREST

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

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Safety and feasibility of hybrid tracheostomy

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Background: Percutaneous dilatational tracheostomy (PDT) is widely used in intensive care units, but this conventional method has some disadvantages, such as requirement of a lot of equipment and experts at the site. Especially, in situations where the patient is isolated due to an infectious disease, difficulties in using the equipment may occur, and the number of exposed persons may increase. In this paper, we introduce hybrid tracheostomy that combines the advantages of surgical tracheostomy and PDT and describe our experiences.

Methods: Data from 55 patients who received hybrid tracheostomy without bronchoscopy from January 2020 to February 2021 were collected and reviewed retrospectively. Hybrid tracheostomy was performed at the bedside by a single thoracic surgeon. The hybrid tracheostomy method was as follows: after the skin was incised and the trachea was exposed, only the extent of the endotracheal tube that could not be removed was withdrawn, and then tracheostomy was performed by the Seldinger method using a PDT kit.

Results: The average age was 66.5 years, and the proportion of men was 69.1%. Among the patients, 21.8% were taking antiplatelet drugs and 14.5% were taking anticoagulants. The average duration of the procedure was 13.3 minutes. There was no major bleeding, and there was one case of paratracheal placement of the tracheostomy tube.

Conclusions: In most patients, the procedure can be safely performed without any major complications. However, patients with a short neck, a neck burn or patients who have received radiation therapy to the neck should be treated with conventional methods.

Key Words: anticoagulants; bronchoscopy; intensive care units; tracheostomy; ventilator weaning

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INTRODUCTION

Tracheostomy is performed in a significant number of patients treated in the intensive care unit (ICU) for prolonged ventilation or airway maintenance. Ever since percutaneous dilatational tracheostomy (PDT) was first introduced by Ciaglia et al. [1] in 1985, it has become a widely used treatment in ICU settings because it is easier than surgical tracheostomy (ST) and can be performed by the bedside. Bronchoscopy and ultrasound guided PDT are the most commonly used percutaneous techniques [2]. PDT is limited by several contraindications, such as history of previous surgery, difficult neck anatomy, and coagulopathies [3,4]. However, in most other cases, PDT shortens the time interval between the decision about a tracheostomy and the actual procedure, and the complication rate of PDT is similar to that

of ST [4,5].

However, the conventional PDT method using a bronchoscope has some disadvantages, such as requirement of a lot of equipment and experts at the site. Especially, in situations where the patient is isolated due to an infectious disease, difficulties in using the equipment may occur, and the number of exposed persons may increase. For this reason, methods to reduce equipment and manpower, such as PDT using a light wand, are being studied [6,7]. In this paper, we introduce hybrid tracheostomy that combines the advantages of PDT and ST based on our experiences.

KEY MESSAGES

- Hybrid tracheostomy is a method that combines the advantages of percutaneous dilatational tracheostomy and surgical tracheostomy, and it does not need a lot of equipment and experts at the site.
- Hybrid tracheostomy can be safely performed without any serious complications in most patients, and it is thought to be a possible treatment for patients taking antiplatelets or anticoagulants.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of Konyang University Hospital (IRB No. 2021-02-010), and the requirement for informed consent was waived due to the retrospective nature of the study. From January 2020 to February 2021, we performed hybrid tracheostomy without bronchoscopy on ICU patients who showed indications for tracheostomy. We collected data from a total of 61 patients who received hybrid tracheostomy and reviewed them retrospectively. We gleaned data, including age, sex, body mass index (BMI), complications, antiplatelets and anticoagulants use, blood test results on the day of the procedure, and the reason for tracheostomy. We investigated the procedure, tube size, and immediate complications that occurred on the day of the procedure, as well as data related to the procedure. The duration of the procedure was defined as the time from skin incision to cannulation. Immediate complications were subdivided into oozing at the tracheostomy site, major bleeding requiring blood transfusion or surgical treatment, paratracheal placement of the tracheostomy tube, and pneumothorax. Finally, as shown in Figure 1, we analyzed the data of 55 patients, after excluding two patients with incorrect data and four patients who underwent the procedure with bronchoscopy out of the 61 patients who received hybrid tracheostomy.

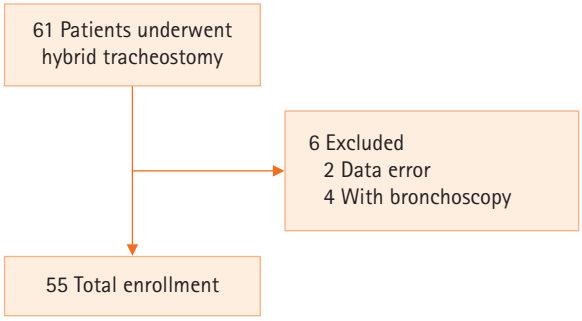

Figure 1. Flowchart showing selection of study population.

Hybrid tracheostomy was performed at the bedside by a single thoracic surgeon. Hybrid tracheostomy was performed in the following manner. After sedation and relaxation using midazolam and vecuronium, the patient's neck extension and surgical draping were performed, and then the skin was incised under local anesthesia. The skin was incised at about 1.0–2.0 cm below the cricoid cartilage in the transverse direction. After making the skin incision, the pretracheal tissue was dissected to expose the trachea. The tube was withdrawn only to the extent of the endotracheal tube that could not be removed. To determine the safe depth for withdrawing the endotracheal tube, we performed a pilot study using bronchoscopy. According to the results, tube withdrawal was safe to a depth of 16–18 cm at upper incisors. Hence, we withdrew the tube up to a depth of 16 cm at upper incisors. No desaturation event occurred. After that, tracheostomy was performed using the PDT kit (Ciaglia Blue Rhino Percutaneous Tracheostomy Introducer Kit; Cook Critical Care, Bloomington, IL, USA) while visually checking the exposed trachea (Figure 2). After all procedures were completed, chest X-rays were taken to check for complications such as pneumothorax. There was one case of traumatic C-spine injury. Hence, in that case, we performed hybrid tracheostomy without neck extension.

RESULTS

A total of 55 patients were sampled, and their baseline characteristics are specified in Table 1. The age of the patients ranged from 18 to 91 years, and the average age was 66.5 years. The male to female ratio was 38 (69.1%) to 17 (30.9%), and the average BMI was 21.8 kg/m^2. The comorbidities of patients were hypertension (34.5%), diabetes mellitus (21.8%), solid

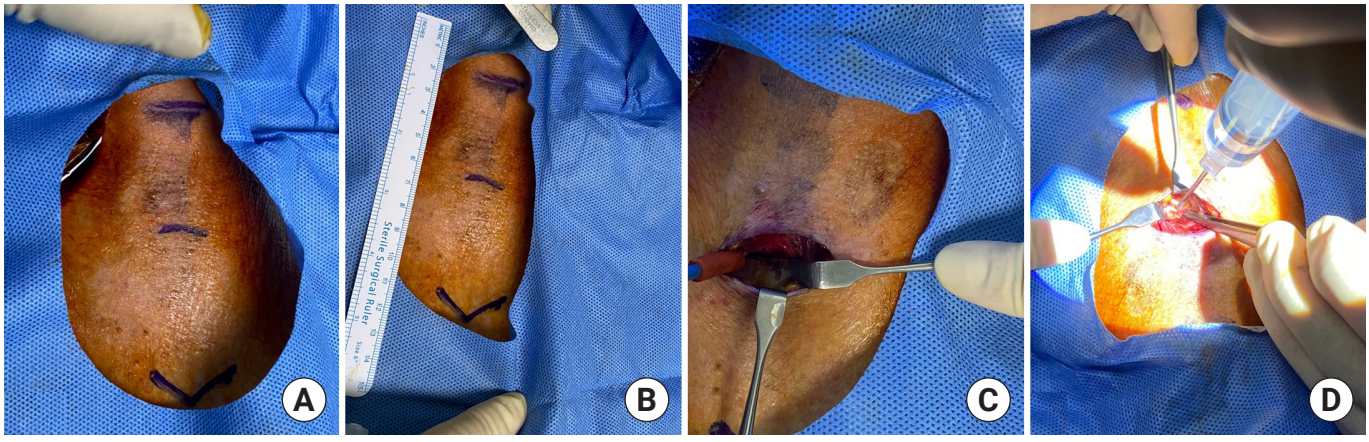

Figure 2. Procedure photo. (A, B) Anatomical position indications. From above, thyroid cartilage, between the 2nd and 3rd tracheal rings, and sternal notch. (C) Exposed trachea by dissecting the pretracheal tissue after skin incision. (D) Photo of performing percutaneous dilatational tracheostomy while visually checking the exposed trachea.

cancer (14.5%), and chronic lung disease (i.e., asthma, chronic obstructive pulmonary disease, and interstitial lung disease; 10.9%). The percentage of patients using antiplatelet drugs was 21.8% and the percentage of those using anticoagulants was 14.5%. None of the patients were taking both antiplatelets and anticoagulant drugs at the same time. Of the patients taking antiplatelet drugs, about a quarter of the patients were using double antiplatelet drugs. The most common reason for admission to the ICU was septic shock (49.1%), followed by respiratory failure excluding respiratory failure due to septic shock (23.6%). Neurological problems leading to ICU admissions included hemorrhage, cerebral infarction, and traumatic C-spine injury. Other reasons include intoxication (herbicides, alcohol), drowning, hanging, and hypovolemic shock due to variable bleeding. A total of 20% of patients underwent tracheotomy to maintain the airways, and 80% of patients underwent tracheotomy due to prolonged mechanical ventilation.

The average duration of the procedure was 13.3 minutes. With respect to the tube size, 7.5 mm was the most used (60%), and 8.0 mm was the next most used (34.5%). The proportion of tracheostomy oozing was 21.8%, and no major bleeding or pneumothorax occurred. Paratracheal placement of the tracheostomy tube occurred in a patient with a short neck with a high BMI of 33.3 kg/m^2 (Table 2).

DISCUSSION

Since PDT is commonly performed at the bedside, the risks and difficulties associated with transporting critically ill patients to the operating room can be avoided [8]. Several studies have suggested that the incidence of delayed complications, such as tracheal stenosis, is similar between ST and PDT [9-11]. Due to these characteristics and ease of the procedure, PDT has become the dominant method of tracheostomy in many centers [8,12,13]. However, conventional PDT has a problem as it requires a lot of equipment and manpower. Especially in infectious diseases, we need to consider how we can solve the problem. In coronavirus disease 2019 (COVID-19) patients, it is recommended that tracheostomy should be performed with the least number of personnel and the most experienced operator should perform the procedure to reduce the number of expose personnel and exposure time [14,15].

This study was conducted to confirm the safety and feasibility of the procedure by analyzing all hybrid tracheostomy cases performed in the ICU for 1 year. In this study, hybrid tracheostomy showed several advantages. First, it did not require a lot of manpower and equipment. Second, the procedure could be executed in a short time of about 13 minutes. Considering the above advantages, we think that the hybrid tracheostomy can be a good method for tracheostomy in infectious diseases. This is because compared to the surgical method, the operation time is short, and compared to the conventional PDT, less manpower is required. It means that the exposure time is short, and the number of people exposed is small. Third, no major bleeding events occurred, although approximately one-third of the patients were using antiplatelets or anticoagulants. The proportion of oozing at the tracheostomy site was slightly higher (21.8%), but we presume that this result was obtained because we included all cases in which blood oozing was adequate enough to change the gauze after the procedure based

Table 1. Baseline characteristics

Variable	Value (n=55)
Age (yr)	66.5 (18.0–91.0)
Male	38 (69.1)
Body mass index (kg/m^2)	21.8 (15.6–33.3)
Comorbidity	
Hypertension	19 (34.5)
Diabetes mellitus	12 (21.8)
Malignancy, solid	8 (14.5)
Chronic lung disease[a]	6 (10.9)
Use of antiplatelet agent	12 (21.8)
Single agent	9 (16.4)
Dual agents	3 (5.5)
Use of anticoagulation agent	8 (14.5)
Low molecular weight heparin	2 (3.6)
Direct oral anticoagulants	1 (1.8)
Nafamostat	5 (9.1)
Lab results on the day of procedure	
Hb (g/dl)	9.96 (7.5–14.9)
HCT (%)	30.6 (23.2–45.7)
PLT (×10^3/mm^3)	209.4 (37.0–584.0)
PT (sec)	14.4 (10.9–23.6)
PT-INR	1.28 (1.00–2.08)
aPTT (sec)	32.7 (23.9–53.6)
Reason for admission to intensive care unit	
Acute cardiac event	2 (3.6)
Sepsis or septic shock	27 (49.1)
Respiratory failure (excluding sepsis/septic shock)	13 (23.6)
Neurologic condition	7 (12.7)
Others[b]	6 (10.9)
Reason for tracheostomy	
Need for long-term free airway maintenance	11 (20.0)
Prolonged mechanical ventilation	44 (80.0)

Values are presented as average (range) or number (%).
Hb: hemoglobin; HCT: hematocrit; PLT: platelet count; PT: prothrombin time; INR: international normalized ratio; aPTT: activated partial thromboplastin time.
[a]Chronic obstructive pulmonary disease, asthma, interstitial lung disease; [b]Intoxication, drowning, hanging, hypovolemic shock due to variceal bleeding.

Table 2. Procedure related data

Variable	Value (n=55)
Duration of procedure (min)	13.3 (4–30)
Tube size (mm)	
7.0	3 (5.5)
7.5	33 (60.0)
8.0	19 (34.5)
Immediate complication	
Oozing at the tracheostomy site	12 (21.8)
Major bleeding	0
Paratracheal placement of tracheostomy tube	1 (1.8)
Pneumothorax	0

Values are presented as average (range) or number (%).

on the records. However, none of the patients required additional hemostatic procedures. However, since there was one case in which the tracheostomy tube was positioned incorrectly in a patient with a short neck and high BMI, it may be difficult to perform this procedure in the following cases: patients with short neck, neck burns, or those who have received neck radiation therapy.

This study has some limitations. First, we were not able to evaluate the long-term complications of this procedure. Second, direct comparison with conventional PDT or ST was not possible because there was no control group. Further, the sampling area was small. Therefore, further research is needed. The final limitation was that surgeons may be more familiar with hybrid tracheostomy than medical intensivist. However, it is not a complicated procedure because the operator only needs to dissect minimal pretracheal tissue to check the trachea. Hence, we think that this method can be performed by any intensivist who can perform conventional PDT methods.

In conclusion, hybrid tracheostomy can be safely performed without any serious complications in most patients. It can also be considered to be a possible treatment for patients taking antiplatelets or anticoagulants without any major complications. It can be a good method in infectious disease because it can reduce the number of exposure personnel and exposure time. However, anatomic considerations, which include but are not limited to short neck, are necessary as patients with a short neck or anatomically difficult structure should undergo ST or PDT with bronchoscopy.

CONFLICT OF INTEREST

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

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AUTHOR CONTRIBUTIONS

Conceptualization: GWK. Data curation: DK. Methodology: JWS, GWK. Project administration: SJK, GWK. Visualization: DK, IBJ. Writing–original draft: all authors. Writing–review & editing: all authors.

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Under or overpressure: an audit of endotracheal cuff pressure monitoring at the tertiary care center

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Background: Mechanical ventilation is a lifesaving intervention for critically ill patients but can produce the major complication of ventilator-associated pneumonia (VAP). Inappropriately inflated endotracheal tubes cause potential harm due to high or low pressure; this can be prevented through monitoring protocols.

Methods: A cross-sectional study of 348 cuff pressure readings was performed with intubated and mechanically ventilated patients to evaluate the exact proportion of patients in intensive care units (ICUs) where the cuff pressure is optimal and to identify the ICUs where device-based monitoring is available to produce a lower proportion of sub-optimal cuff pressure cases. Every three days, cuff pressure was assessed with a handheld cuff pressure manometer. The corresponding VAP rates of those ICUs were obtained from the hospital infection control department.

Results: Cuff pressure of 40.2% was the lower cutoff for the high category, that of optimal was 35.3%, and the highest cutoff of sub-optimal was 24.4%. This study also showed ICUs that had cuff pressure monitoring devices and protocols. Active measurement protocols had a higher proportion of optimal cuff pressure (58.5%) and a lower proportion of sub-optimal and high cuff pressure (19.5% and 22.0%) compared to ICUs with no device-based monitoring protocols. Furthermore, the VAP rate of ICUs exhibited a weak positive correlation with sub-optimal cuff pressure.

Conclusions: Device-based cuff pressure monitoring is essential in maintaining adequate cuff pressure but often is inadequate, resulting in high readings. Therefore, this study suggests that device-based cuff pressure monitoring be practiced.

Key Words: airway management; artificial respiration; endotracheal; hospital acquired pneumonia; intubation; mechanical ventilation; ventilator-associated pneumonia

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INTRODUCTION

Mechanical ventilation is a lifesaving intervention for critically ill patients. Even though this maneuver can help critically ill patients with associated risk factors, it contributes to difficult treatment process and weaning. Among the 427 health care-associated infections observed, pneumonia was the most common, and 32% of those cases were ventilator-associated [1]. A large number of patients receiving mechanical ventilation are initially treated with an endo-tracheal tube as a dependable entry point to the airway. The end of this connecting tube is

attached to an air-filled balloon and positioned snuggly in the trachea to prevent air leaks and aspiration [2,3]. The air-filled balloon often is called an endo-tracheal cuff, and the pressure is referred to as endo-tracheal cuff pressure and must be in a safe range of 20–30 cm H_2O to ensure delivery of ordered mechanical ventilation and tidal volume. Proper pressure can decrease the risk for aspiration of secretions that accumulate above the cuff and maintains adequate tracheal perfusion. There is no acceptable practice for measuring cuff pressure even though it has been shown that a cuff pressure below 20 cm H_2O contributes to a fourfold risk of occurrence of ventilator-associated pneumonia (VAP) among the critically ill [2-6].

There are various elements contributing to VAP from which cuff pressure monitoring can be performed by registered nurses and can have help prevent VAP [7]. However, there are no direct studies to establish the importance of nurse-led cuff pressure monitoring and its impact on VAP prevention. Therefore, the study aim was to determine the exact proportion of patients in intensive care units (ICUs) with optimal cuff pressure, identify the ICUs where device-based monitoring is available to achieved a lower proportion of patients with sub-optimal cuff pressure, and to find the correlation of VAP rate in ICUs with the proportion of patients who exhibited optimal cuff pressure.

KEY MESSAGES

- This study demonstrated that intensive care units intensive care units (ICUs) with cuff pressure monitoring devices and active measurement protocols had a higher proportion of patients with optimal cuff pressure (58.5%) and a lower proportion with sub-optimal and high cuff pressures (19.5% and 22.0%) compared to ICUs with no device-based monitoring protocols.
- The ventilator-associated pneumonia rates of ICUs exhibited a weak positive correlation with sub-optimal cuff pressure.

MATERIALS AND METHODS

Permission was obtained from the Jawaharlal Institute of Postgraduate Medical Education and Research Ethical Committee, Human Studies (Reg. No. JIP/IEC/2018/079). Ethical issues involved were minimal. Informed consent was obtained from every participant's parent/legally authorized/acceptable representative since they could not provide consent because of critical illness and inability/unconsciousness after a brief explanation regarding the study by the investigator. Confidentiality of the data, the right to withdraw from the study, and anonymity of the subjects were explained before data collection. Good Clinical Practice guidelines of the Indian Council for Medical Research were followed. Patient data were stored confidentially.

Prospective cross-sectional audit of intubated and mechanically ventilated patients in ICUs of a tertiary care hospital was performed. This audit was carried out every three days in 11 ICUs of a tertiary care hospital between August 2019 to November 2019 in patients who were intubated with a cuffed endotracheal tube (ETT) and mechanically ventilated in the ICUs on the day of the visit. The date and time of the visits were determined randomly using a computer spreadsheet program so that any changes in practice (that is, adjusting the cuff pressure in anticipation of the visit) caused by the study were minimized. The study excluded patients intubated with non-air cuffed ETTs where pressure cannot be measured and non-invasively ventilated patients without ETT.

The device that was used for sample collection was a COVIDIEN-Shiley Hi-Lo Hand pressure Gauge (VBM Medizintechnik, Sulz am Neckar, Germany). Cuff pressure readings were obtained by connecting the pilot balloon to the cuff pressure manometer. The normal pressure range of 20–30 cm H_2O was considered optimal cuff pressure, <20 cm H_2O was sub-optimal, and high cuff pressure was >30 cm H_2O. Exact readings were documented in an online data entry sheet (google sheet). When the investigator observed that the pressure was too high or too low, it was immediately corrected using the same device, or the assigned nursing personnel was notified to correct it since it is unethical to leave the cuff pressure at suboptimal level. Multiple measurements were performed from a single patient if they continued to be on a ventilator for a longer period. These additional measurements did not affect the study since the investigators were only studying the proportion of instances of the cuff pressure measurements of beds in an ICU where the cuff pressures and VAP rates were normal according to the number of hours of ventilation days rather than per patient.

The institute has a dedicated team of infection control nurses who collect VAP rates based on everyday clinical assessments with updated Centers for Disease Control and Prevention diagnostic criteria. The investigators accessed VAP rate data per month from the infection control department. These rates were calculated every month, and data of a particular month were used when the investigator had performed cuff

pressure measurements. Since the measurements were performed for 4 months, investigators calculated the average of the VAP rates and correlated it with cuff pressure.

A primary survey was conducted every month in the ICUs during the course of the study to determine whether the ICUs were using a cuff pressure monitor or if one was available and if there was an active usage protocol. The study also surveyed some of the other confounding factors that can affect VAP rates like head end elevation, availability of bed side hand rubbing, closed suctioning system availability, and nurse to patient ratio in the unit at the time of the survey.

Statistical analysis was carried out using the IBM SPSS ver. 22 (IBM SPSS Inc., Armonk, NY, USA). Frequencies and percentages were used for cuff pressure assessment, and proportions were used to describe the number of patients who had optimal cuff pressure. The Kruskal-Wallis test, Spearman rank correlation, chi-square test, Mann-Whitney test, and Fisher's exact test were used to summarize the data. All the statistical tests were carried out at a 5% level of significance, and a P-value less than 0.05 was considered significant.

RESULTS

The survey obtained 348 discreet cuff pressure readings from mechanically ventilated patients from 11 ICUs. The ICUs that had a smaller number of cuff pressure readings were combined for interpretation (ICUs that contributed less than 15 cuff pressure readings combined were obstetrics and gynecology ICU [n=2], plastic surgery ICU [n=9], respiratory care center ICU [n=1], surgical ICU [n=14], and urology ICU [n=3]). Among the 348 cuff pressure readings obtained, the majority of the readings were in the high cuff pressure category at 140 (40.2%), optimum cuff pressure was at 123 (35.3%), and sub-optimal cuff pressure was at 85 (25%).

Table 1 indicates that the most frequent sub-optimal cuff pressure readings were observed in the neuromedicine ICU at 42.1% (n=16) and the fewest were noted in the emergency medical services high dependency unit at 15.6% (n=10). High cuff pressure readings were more prominent in the survey where most of the cuff pressure readings were obtained from the emergency medical services (EMS) high dependency unit (HDU) at 59.4% (n=38). A smaller number of high cuff pressure readings was found in the neurotrauma ICU, at 16.7% (n=10). The maximum number of optimal-cuff pressure readings were obtained from the Neurotrauma ICU at 65% (n=39), and the minimum was recorded in the neuro-medicine ICU at 21.1% (n=8).

Another result of the audit showed that only two of the total 11 ICUs that participated had a dedicated device for monitoring and an active measurement protocol (AMP). Therefore, 76.44% (n=266) cuff pressure readings were obtained from ICUs where there was no device for monitoring and no AMP. Only 23.56% (n=82) were obtained from ICUs that had dedicated equipment and AMP for monitoring. These findings were reflected in the cuff pressure distribution among the categories, as depicted in Table 2, which shows a significant association between AMP and cuff pressure category (P=0.001). ICUs with monitoring had lower proportions of sub-optimal (19.5%) and high (22.0%) cuff pressure compared to those without AMP (25.9% and 45.9%, respectively). The proportion of optimal cuff pressure (58.5%) was greater in ICUs with AMP compared to those that did not (28.2%). Our results showed a weak positive correlation of sub-optimal cuff pressure with VAP rate, as depicted in Table 3. In addition, we identified

Table 1. Frequency distribution of CP among ICU

ICU	Sub-optimal CP (<20 cm H_2O)	Optimal CP (20–30 cm H_2O)	High CP (>30 cm H_2O)
CTVS ICU (n=49)	16 (32.7)	16 (32.4)	17 (34.7)
EMS HDU (n=64)	10 (15.6)	16 (25.0)	38 (59.4)
EMS ICU (n=83)	15 (18.1)	25 (30.1)	43 (51.8)
Neuromedicine ICU (n=38)	16 (42.1)	8 (21.1)	14 (36.8)
Neurosurgery ICU (n=25)	5 (20.0)	11 (44.0)	9 (36)
Neuro trauma ICU (n=60)	11 (18.3)	39 (65.0)	10 (16.7)
Other ICUs (n=29)[a]	12 (41.3)	8 (27.58)	9 (31.0)
Total (n=348)	85 (24.4)	123 (35.3)	140 (40.2)

Values are presented as number (%). Total number of cuff pressure measurement=348.
ICU: intensive care unit; CP: cuff pressure; CTVS: cardio thoracic and vascular surgery; EMS: emergency medical services; HDU: high dependency unit.
[a]ICUs where less than 15 cuff pressure measurements were made and those ICUs are the following respective: ICU, surgical ICU, obstetrics and gynaecology ICU, plastic surgery ICU, and urology ICU.

Table 2. Association of CP monitor availability and active measurement protocol with cuff pressure category

Group	CP category			P-value[a]
	Sub-optimal CP (<20 cm H_2O, n=85)	Optimal CP (20–30 cm H_2O, n=123)	High CP (>30 cm H_2O, n=140)	
Cuff pressure monitor & active measurement protocol				0.001[b]
No (n=266)	69 (25.9)	75 (28.2)	122 (45.9)	
Yes (n=82)	16 (19.5)	48 (58.5)	18 (22.0)	

Values are presented as number (%).
CP: cuff pressure.
[a]Chi-square test; [b]P<0.05.

Table 3. Correlation of VAP rate with cuff P category among mechanically ventilated patients in ICUs where the P stands for pressure

Variable	No. (%)	r^a	P-value
Sub-optimal CP (<20 cm H_2O)	85 (24.4)	0.214	0.04[b]
Optimal CP (20–30 cm H_2O)	123 (35.3)	–0.076	0.40
High CP (>30 cm H_2O)	140 (40.2)	0.109	0.20

VAP: ventilator-associated pneumonia; ICU: intensive care unit; CP: cuff pressure.
[a]Spearman rank correlation coefficient; [b]P<0.05.

Table 4. Distribution of confounding factors for ventilator associated pneumonia during cuff pressure measurements

Variable	No. (%)
Availability of closed suction among cuff pressure measured	
No	327 (94)
Yes	21 (6.0)
Hand rub availability	
No	96 (27.6)
Yes	252 (72.4)
Nurse patient ratio	
1:2	5 (1.4)
1:3	277 (79.6)
1:5	6 (1.7)
1:6	2 (0.6)
1:10	58 (16.7)
Head end elevation	
Low (head elevation <30°)	134 (38.5)
Normal (head elevation –30 to –45°)	197 (56.6)
High (head elevation >45°)	17 (4.9)

some confounding factors of VAP, as provided in Table 4.

DISCUSSION

The present study showed that most of the cuff pressure values were high, at a percentage of 40.2% (n=140), while optimal cuff and sub-optimal cuff pressures were found in 35.3% and 24.4% of patients, respectively. A high cuff pressure can compromise perfusion and cause impairments in the wall of the trachea and adjacent anatomical structures [5,8,9]. Therefore, need for an effective cuff pressure measuring protocol and device-based monitoring is high.

A cuff pressure greater than 30 cm H_2O is enough to compromise the anterolateral trachea, affect microcirculation, and lead to multiple complications such as sore throat, hoarseness, stenosis of the trachea, rupture of the trachea, injury, and tracheal esophageal fistula [6,10-12]. Several studies surveyed endo-tracheal tube cuff pressure monitoring and found a similar higher incidence of high cuff pressure in emergency departments [13,14].

Our results also showed that a cuff pressure monitoring device and protocol significantly increased the proportion of patients with optimal cuff pressure and reducing the sub-optimal cuff pressure to 19.5% and high cuff pressure 22.0% when compared to those ICU's didn't which did not have the same reported the proportion of sub-optimal cuff pressure as 25.9%, High cuff pressure was 45.9% and Optimal cuff pressure was 28.2% which was significant (P<0.001). A previous quality enhancement study reported concurrent results when using cuff pressure manometers [15]. The cuff pressure range was significant (P=0.0003), and an increase in the safe range of cuff pressure was observed after the introduction of cuff pressure monitoring, AMP, and departmental education. In addition, before implementation, most of the cuff pressure values were high.

There are inadequate data to guide clinicians on the optimal frequency of ETT cuff pressure measurements. Current practices differ throughout the world, from very infrequent to continuous assessments of cuff pressure. However, use of a continuous ETT cuff-pressure control system is associated with significantly lower risk of VAP as it lowers the risk of advancement of subglottic secretions into the lower respiratory tract [16,17].

Temporary drops in endotracheal cuff pressure are important for entry of upper airway secretions into the lower airways and increase in the incidence of VAP. Studies have shown that continuous pressure control and optimal ET cuff pressure minimize leakage of collected secretions that have pooled above the cuff [18]. In this study, we observed a significantly weak positive correlation (r=0.214, P=0.04) of sub-optimal cuff pressure with VAP rate. This can be considered a limitation of the study but without clinical significance. Multivariate analysis performed by Rello et al. [6] also showed a trend toward higher risk of VAP among patients with sub-optimal cuff pressure (relative risk, 2.57; 95% confidence interval, 0.78–8.03).

Furthermore, no continuous data on cuff pressure were maintained to ascertain the relationship, as the primary aim of the study was to establish the relationship between optimal cuff pressure and availability of cuff pressure measurement and AMP [3-5,19].

The main limitation of the present study was that there was no continuous monitoring of cuff pressure and factors that contributed to cuff pressure changes. The study was performed based on instances of measurement and not on individual patients. As a result, the clinical covariates of patients were not considered. This restricted further statistical analysis on the predictors of cuff-pressure variations. Due to the time limitation of the study, unit-wise monthly VAP rate was used for assessing the correlation with cuff pressure since each individual could not be followed-up for the same amount of time. Another limitation was that it was not possible to detect pressure leaks while attaching the device to the pilot balloon during monitoring.

This study suggests provision of cuff pressure monitoring devices for every critical care unit and development of AMP from an administrative level to promote optimal cuff pressure. This will reduce the overall VAP rates in hospitals. Adherence to the protocol can be added as a quality indicator hospital infection control.

CONFLICT OF INTEREST

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

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Conceptualization: BV, MJK, GK. Data curation: BV. Formal analysis: BV, MJK, GK. Methodology: MJK, GK. Project administration: BV, MJK, GK. Visualization: all authors. Writing–original draft: BV, MJK, GK. Writing–review & editing: all authors.

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Prognostic factors of pediatric hematopoietic stem cell transplantation recipients admitted to the pediatric intensive care unit

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Background: Pediatric patients who received hematopoietic stem cell transplantation (HSCT) tend to have high morbidity and mortality. While, the prognostic factors of adult patients received bone marrow transplantation were already known, there is little known in pediatric pateints. This study aimed to identify the prognostic factor for pediatric intensive care unit (PICU) mortality of critically ill pediatric patients with HSCT.

Methods: Retrospectively reviewed that the medical records of patients who received HSCT and admitted to PICU between January 2010 and December 2019. Mortality was defined a patient who expired within 28 days.

Results: A total of 131 patients were included. There were 63 boys (48.1%) and median age was 11 years (interquartile range, 4–15 years). The most common HSCT type was haploidentical (38.9%) and respiratory failure (44.3%) was the most common reason for PICU admission. Twenty-eight-day mortality was 22.1% (29/131). In comparison between survivors and non-survivors, the number of HSCTs received, sepsis, oncological pediatric risk of mortality-III (OPRISM-III), pediatric risk of mortality-III (PRISM-III), pediatric Sequential Organ Failure Assessment (pSOFA), serum lactate, B-type natriuretic peptide (BNP) and use of mechanical ventilator (MV) and vasoactive inotropics were significant predictors ($P<0.05$ for all variables). In multivariate logistic regression, the number of HSCTs received, use of MV, OPRISM-III, PRISM-III and pSOFA were independent risk factors of PICU mortality. Moreover, three scoring systems were significant prognostic factors of 28-day mortality.

Conclusions: The number of HSCTs received and use of MV were more accurate predictors in pediatric patients received HSCT.

Key Words: hematopoietic stem cell transplantation; mortality; pediatric intensive care unit; prognosis

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INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is currently used as a treatment for high-risk or relapsed hematologic malignancies and non-malignant hematologic disease [1,2]. For successful transplantation, recipients have to overcome several complications such as sepsis, graft versus host disease (GVHD), thrombotic microangiopathies, and veno-occlusive

disease that occur after HSCT [3-5]. To prevent complications, the HSCT protocol has been reorganized across areas such as precise human leukocyte antigen (HLA) typing, graft manipulation, conditioning regimen, prophylactic antibiotics, or antifungal agents [5-8]. Also, intensive care management has been improved with time [9]. However, a significant proportion of adult and pediatric recipients still become critically ill, requiring admission to the intensive care unit (ICU). Many factors, including preexisting disease, transplant-related toxicity, infection, and sequelae of pre- or post-transplant organ damage, are thought to be contributory.

As the number of HSCTs patients increases, the number of patients admitted to the ICU also increases. Thus, many investigators are working on identifying the prognostic factors of ICU mortality. Several HSCT-related factors, such as underlying disease, type of HLA mismatch, failure of neutrophil engraftment, presence of GVHD, and cytomegalovirus (CMV) seropositivity are associated with increased mortality after HSCT [10-12]. Critical care interventions, such as mechanical ventilator (MV), renal replacement therapy, vasoactive inotropes were known to be the significant factors of mortality [13]. Moreover, many studies have assessed the correlation between scoring systems, such as the Acute Physiology and Chronic Health Evaluation (APACHE) II, Simplified Acute Physiology Score (SAPS), and Sequential Organ Failure Assessment (SOFA) scores, and mortality in adults [11,14]. However, for pediatric patients, only a few such studies have assessed the severity of illness in HSCT patients as a prognostic factor, and there are only a few studies on the reappraisal of pediatric HSCT recipients. Pedaitric HSCT patients have increased severity in a variety of forms when they admit pediatric intensive care unit (PICU) and the prognostic factors resulting from mortality have been also rarely studied. Thus, we reviewed that the critical ill pediatric patients admitted to the ICU to identify the significant risk factors, especially severity illness of scores, which can predict mortality.

KEY MESSAGES

- Pediatric patients who received hematopoietic stem cell transplantation (HSCT) tend to have several complications and have high mortality.
- The number of HSCTs received, use of mechanical ventilator, oncological pediatric risk of mortality-III (OPRISM-III), pediatric risk of mortality-III (PRISM-III), and pediatric Sequential Organ Failure Assessment (pSOFA) were significant prognostic factor of 28-day mortality.

MATERIALS AND METHODS

Patients

We investigated all HSCT recipients admitted to the 14-bed multidisciplinary PICU of Asan Medical Center Children's Hospital, Seoul, Korea between January 2010 and December 2019. We excluded patients who had insufficient data necessary for severity scoring and patients with a Do-Not-Resuscitate order in place. The Institutional Review Board of the Asan Medical Center approved this study (IRB No. 2020-0382) and parental consent was waived due to the retrospective nature of the analyses.

Data Collection

We retrospectively reviewed the electrical medical records of the enrolled patients and obtained data, including age at PICU admission, sex, underlying hemato-oncologic disease, length of PICU stay, and mortality. The HSCT parameters, including HSCT type, development of acute GVHD, CMV infection, veno-occlusive disease, and transplant-associated thrombotic microangiopathy were evaluated. The clinical and biological variables, including vital signs, arterial blood gas analysis, and laboratory results, such as complete blood count, chemistry profiles, coagulation profiles, and C-reactive protein, serum lactic acid, and B-type natriuretic peptide (BNP) levels were analyzed. For identifying the severity of disease, we used the oncological pediatric risk of mortality-III (OPRISM-III), pediatric risk of mortality-III (PRISM-III), and pediatric Sequential Organ Failure Assessment (pSOFA) scores calculated within 24 hours of PICU admission. The PRISM-III consists of cardiovascular/neurologic vital signs, acid-base/blood gas values, and chemical (glucose, creatinine, potassium, and blood urea nitrogen), and hematologic laboratory values (white blood cell count, platelet count, and coagulation profile) [15]. The pSOFA comprises the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2/FiO_2) ratio, platelet count, bilirubin level, mean arterial pressure (MAP) or vasoactive infusion, Glasgow coma scale (GCS) score, and creatinine level [16]. The PRISM-III and pSOFA were often used to evaluate multiorgan failure in critically-ill pediatric patients, and the OPRISM-III, a modification of the PRISM-III, was used for assessing children after HSCT [17]. During ICU management, the need for invasive MV, continuous renal replacement therapy, and vasoactive inotropic drugs were monitored. Mortality was

defined as a patient who died within 28 days during the PICU stay. The primary outcome was the PICU 28-days mortality and the secondary outcome was risk factors that predisposed to mortality.

Statistical Analysis

All data were analyzed using the IBM SPSS ver. 21.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as median with interquartile range or mean±standard deviation and a two-tailed Student t-test, as appropriate. We used the chi-square or two-tailed Fisher's exact tests to analyze categorical variables. We used the multivariate logistic regression analysis to interrogate variables to find independent risk factors. We calculated the area under the curve (AUC) and the

Table 1. Baseline characteristics of the study population

Variable	Total (n=131)	Survivor (n=102)	Non-survivor (n=29)	P-value
Male	63 (48.1)	50 (49)	13 (44.8)	0.690
Age at HSCT	9.46 (3.14–14.79)	9.54 (2.63–14.84)	9.46 (3.26–15.42)	0.939
Age at PICU admission	11.00 (4.00–15.00)	11.00 (4.00–25.00)	9.00 (3.00–15.00)	0.233
Length of PICU stay (day)	16.94±27.43	19.54±30.34	7.79±7.87	0.041
Underlying hemato-oncologic disease				0.731
Leukemia	67 (51.1)	53 (52)	14 (48.3)	
Lymphoma	7 (5.3)	6 (5.9)	1 (3.4)	
Non-malignant hematologic disease	26 (19.8)	21 (20.6)	5 (17.2)	
Solid tumor	31 (23.7)	22 (21.6)	9 (31)	
Types of donor				0.160
HLA matched (related)	9 (6.9)	9 (8.8)	2 (6.9)	
HLA matched (unrelated)	37 (28)	31 (30.4)	4 (13.8)	
HLA mismatched (related)	53 (40.4)	35 (34.3)	16 (55.2)	
HLA mismatched (unrelated)	5 (3.8)	5 (4.9)	0	
Autologous	27 (20.6)	20 (19.6)	7 (24.1)	
No. of HSCTs				0.013
1	106 (80.9)	88 (86.3)	18 (62.1)	
≥2	25 (19.1)	14 (13.7)	11 (37.9)	
Day from HSCT to admission				0.064
<30	21 (16.0)	14 (13.7)	7 (24.1)	
31–99	23 (17.6)	15 (14.7)	8 (27.6)	
>100	87 (66.4)	73 (71.6)	14 (48.3)	
Main reason for PICU admission				0.460
Respiratory failure	58 (44.3)	45 (44.1)	13 (44.8)	
Neurologic defect	18 (13.7)	12 (11.8)	6 (20.7)	
Sepsis	17 (13.0)	13 (12.7)	4 (13.8)	
Renal failure	12 (9.2)	10 (9.8)	2 (6.9)	
Hemato-oncology complication	12 (9.2)	10 (9.8)	2 (6.9)	
Cardiovascular disease	7 (5.3)	7 (6.9)	0	
Gastro-intestinal disease	7 (5.3)	5 (4.9)	2 (6.9)	
CMV infection	35 (26.7)	29 (28.4)	6 (20.7)	0.406
Veno-occlusive disease	9 (6.9)	7 (6.9)	2 (6.9)	0.995
Graft-versus-host disease	28 (21)	18 (17.6)	10 (34.5)	0.135
TA-TMA	13 (9.9)	11 (10.8)	2 (6.9)	0.537
Septic shock	17 (13.0)	13 (12.7)	4 (13.8)	0.022

Values are presented as number (%), median (interquartile range), or mean±standard deviation.
HSCT: hematopoietic stem cell transplantation; PICU: pediatric intensive care unit; HLA: human leukocyte antigen; CMV: cytomegalovirus; TA-TMA: transplant-associated thrombotic microangiopathy.

DeLong test was used to compare the performance between two assays based on the AUC of receiver operating characteristics (ROC) curves. We obtained appropriate cut-off values and analyzed data according to the maximum value of the Youden index. Survival curves were performed using the Kaplan-Meier methodology and the log-rank test was used to compare variables. All variables with a P-value of less than 0.05 were considered statistically significant.

RESULTS

Patients

A total of 2858 children were admitted to the PICU from 2010 to 2019, and 131 received HSCT. The demographic characteristics of the patients are presented in Table 1. There were 63 boys (48.1%), and the median age of the patients admitted to the PICU was 11 years (interquartile range, 4–15 years). The most common underlying hemato-oncologic diagnosis was leukemia (n=67, 51.1%). A total of 104 (79.4%) allogeneic and 27 (20.6%) autologous bone marrow transplantation (BMT) procedures were performed. The median period from HSCT to admission was 197±84 days (0–3,658 days). The period from HSCT to admission was more than 100 days for 66.4% of the patients; 30–99 days, 17.6% and <30 days, 16%. The most commonly noted reasons for PICU admission was respiratory failure (n=58, 44.3%), followed by neurologic defects (n=18, 13.7%) and sepsis (n=17, 13.0%).

Demographics and Comparisons between Survivors and Non-survivors

The 28-day mortality rate was 22.1% (29/131). With respect to the baseline characteristics, the number of BMT and presence of septic shock were the significant factors affecting mortality (P=0.013 and P=0.031, respectively) (Table 1). As shown in Table 2, the severity of illness scores (OPRISM-III, PRISM-III, and pSOFA) and several laboratory values (serum lactic acid, and BNP level) at PICU admission were the significant prognostic factors. In terms of treatments administered within the first day of PICU admission, the use of MV and vasopressors was associated with mortality (P=0.011 and P=0.042, respectively).

Multivariate Logistic Regression Analysis

The result of univariate logistic regression was the same as the result of the comparison between survivors and non-survivors. However, in multivariate analysis adjusted for other potentially confounding independent variables, the number of HSCTs received (P<0.05), use of MV (P<0.05), OPRISM-III (odds ratio [OR], 1.137; 95% conficdence interval [CI], 1.074–1.204; P<0.001), PRISM-III (OR, 1.144; 95% CI, 1.0771.215; P<0.001) and pSOFA (OR, 1.222; 95% CI, 1.078–1.385; P=0.002) were independent predictors of PICU mortality in separate logistic equations (Table 3).

ROC Curve and Kaplan-Meier Analysis

We found that the value of the area under the ROC (AUROC) curve of the three severity of illness scores were all associated

Table 2. Laboratory values, severity of illness scores, and treatment on the first day of PICU

Variable	Total (n=131)	Survivor (n=102)	Non-survivor (n=29)	P-value
OPRISM-III	21.15±10.97	18.23±8.76	31.45±11.87	<0.001
PRISM-III	19.28±10.28	16.53±8.14	28.97±11.26	<0.001
pSOFA	7.24±3.99	9.06±3.57	12.38±4.56	0.001
Glasgow coma scale	10.66±4.46	1.57±1.48	2.21±1.86	0.097
Creatinine (mg/dl)	0.97±0.89	0.96±0.90	1.00±0.87	0.842
Total bilirubin (mg/dl)	2.47±6.42	2.21±6.93	3.38±4.15	0.390
Lactic acid (mmol/L)	3.79±3.93	2.79±2.73	7.31±5.31	<0.001
CRP (mg/dl)	11.85±11.78	11.47±11.32	13.26±13.45	0.478
BNP (pg/ml)	607.86±960.81	578.73±924.68	1,450.20±1,613.22	0.015
Use of mechanical ventilator	82 (62.6)	58 (56.9)	24 (82.8)	0.011
Use of vasoactive inotropic agents	51 (38.9)	35 (34.3)	16 (55.2)	0.042
Use of renal replacement therapy	36 (27.5)	27 (26.5)	9 (31)	0.627

Values are presented as mean±standard deviation or number (%).
PICU: pediatric intensive care unit; OPRISM-III: oncological pediatric risk of mortality-III; PRISM-III: pediatric risk of mortality-III; pSOFA: pediatric Sequential Organ Failure Assessment; CRP: C-reactive protein; BNP: B-type natriuretic peptide.

Table 3. Multivariate logistic regression analysis for the prediction of PICU mortality

Variable	Multivariate (model 1)		Multivariate (model 2)		Multivariate (model 3)	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
No. of HSCTs	3.368 (1.297–8.747)	0.013	3.045 (1.190–7.792)	0.02	3.532 (1.435–8.678)	0.006
Septic shock	0.794 (0.175–3.598)	0.765	1.028 (0.207–5.092)	0.973	0.917 (0.225–3.730)	0.903
OPRISM-III	1.142 (1.080–1.208)	<0.001				
PRISM-III			1.148 (1.082–1.218)	<0.001		
pSOFA					1.250 (1.109–1.409)	<0.001

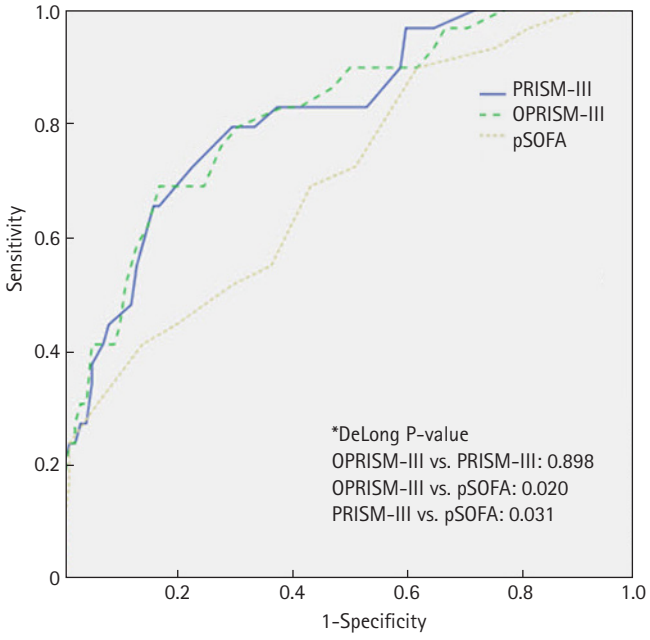
PICU: pediatric intensive care unit; HR: hazard ratio; CI: confidence incidence; HSCT, hematopoietic stem cell transplantation; OPRISM-III: oncological pediatric risk of mortality-III; PRISM-III: pediatric risk of mortality-III; pSOFA: pediatric Sequential Organ Failure Assessment.

with the 28-day mortality, and the AUC value of OPRISM-III score was the largest compared with other severity of illness scores (AUROC, 0.818; 95% CI, 0.731–0.905) (Figure 1). Using the DeLong test, the AUROC value of OPRISM-III and PRISM-III were significantly larger than that of pSOFA. However, there were no significant differences between OPRISM-III and PRISM-III. Then, we calculated the cut-off value of each score by using the AUC and obtained appropriate cut-off values. The cut-off value of OPRISM-III was 21.5, PRISM-III was 19.5, and pSOFA was 11. All scoring systems showed significant differences with respect to the cut-off values associated with the 28-day mortality in the Kaplan-Meier analysis (Figure 2).

DISCUSSION

Although there have been changes in conditioning regimen, immunosuppressive agents due to the complications after HSCT, the mortality that occurs after BMT is still high. According to the result of this study, when comparing the survivors and non-survivors, the number of HSCTs received, septic shock, use of inotropics and MV, severity of illness scores, serum lactic acid and BNP levels were associated with mortality in pediatric patients after HSCT. In multivariate analysis of 28-day mortality, the number of HSCTs done, OPRISM-III, PRISM-III, and pSOFA scores were the independent prognostic factors of 28-day mortality.

The number of HSCTs received and use of MV are already known predictors of mortality, based on previous studies [10,11,13,18-21]. The strength of our study was that the three scoring systems mentioned in each of the different studies are all significant predictors of mortality. Previous pediatric study, the OPRISM and PRISM-III were investigated for predicting mortality [22-27]. Another pediatric study reported that the difference between the maximum pSOFA and admission pSOFA scores was associated with the PICU mortality [28].



Variables	AUROC (95% CI)
PRISM-III	0.816 (0.730–0.903)
OPRISM-III	0.818 (0.731–0.905)
pSOFA	0.704 (0.596–0.812)

Figure 1. Receiver operating characteristics (ROC) curve and result of DeLong test between the area under the curve value of each scoring system. PRISM-III: pediatric risk of mortality-III; OPRISM-III: oncological pediatric risk of mortality-III; pSOFA: pediatric Sequential Organ Failure Assessment; AUROC: area under the receiver operating characteristics; CI: conficdence interval.

Our study differed from the previous pediatric study in that we evaluated the pSOFA score, a useful evaluation tool in recent pediatric critical care, together with OPRISM-III and PRISM-III on PICU admission. Therefore, three scoring systems were all useful tool to predict mortality of critically ill pediatric patients received BMT according to our study.

Previous studies showed that septic shock, use of vasoactive inotropes, and serum lactic acid were good predictors

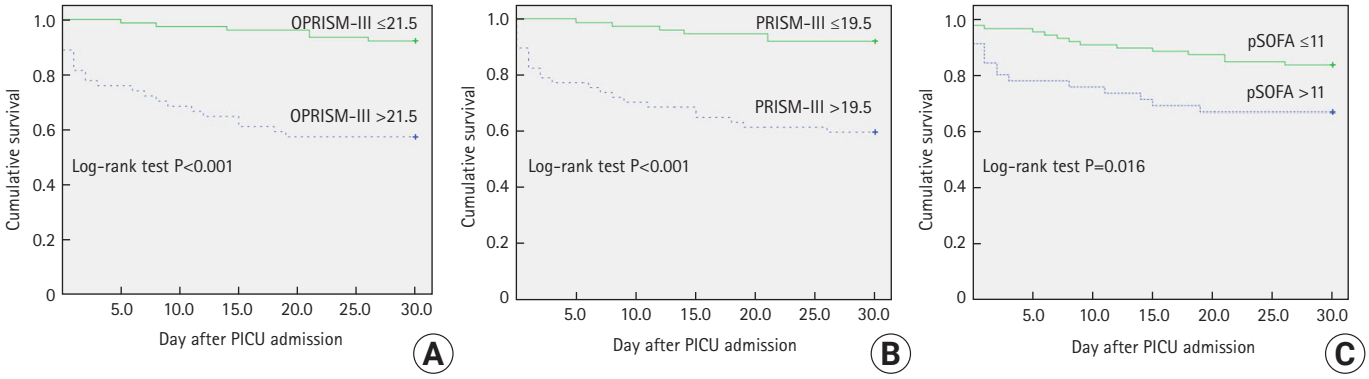


Figure 2. Kaplan-Meier analysis of oncological pediatric risk of mortality-III (OPRISM-III; A), pediatric risk of mortality-III (PRISM-III; B) and pediatric Sequential Organ Failure Assessment (pSOFA; C). All of these three scoring systems have significant difference in 28-day mortality. PICU: pediatric intensive care unit.

between survivors and non-survivors [10,18,23,29]. However, the GCS, creatinine, total bilirubin known mortality predictors in hildren after HSCT were not associated with mortality in our study [19,22,23,27,28,30,31]. When each organ failure is separately investigated, no correlation with the probability of mortality was seen in our study. However, the severity of illness scores at PICU admission, such as the pSOFA score, which includes the GCS score, creatinine, total bilirubin, that showed perfect discriminatory power for the evaluation of multi organ function adjusted for age were significantly higher among the non-survivors [16].

Previous studies have shown that septic shock to be a significant predictor of outcome in HSCT recipients admitted to the ICU [32,33]. In our study, septic shock was not significant factor by using multivariate logistic regression analysis. Because, most septic shock patients had effective response on early fluid therapy and vasopressor administration. Although septic shock is associated with an overall severe course, rapid recovery of specific organ function has been noted due to recent advances and improvements in the management of septic shock in cancer patients [34,35]. Early involvement in septic shock treatment represents that it had less effect on mortality than other organ complications. Rather, multi organ dysfunction on the first day after PICU admission were found to be more important than presence of septic shock at PICU admission.

Heart failure is a known complication of HSCT because of the use of cardiotoxic drugs post-transplantation, notably cyclophosphamide and anthracyclines [36,37]. Therefore, physicians often use BNP to monitor the cardiotoxic effects of medications after HSCT [38]. Although BNP may be a useful predictor of cardiac dysfunction after HSCT, it is not superior to other factors in predicting mortality. Even though we compensated for age-based creatinine levels, it has been confirmed that there is no association between creatinine level and BNP. In terms of vasopressors, several studies have shown that the use of vasopressors had a negative impact on survival in univariate analysis but was not significantly associated with mortality in multivariate analysis when compared with the severity of illness scores, such as APACHE II, SOFA, and OPRISM scores [11,21,23]. In our study, the severity of illness scores, such as PRISM-III and pSOFA scores, which included the systolic blood pressure (SBP) or MAP and the amount of vasoactive infusion as variables, were the independent prognostic factors of the 28-day mortality compared to the use of vasoactive inotropes. This result showed that the amount of inotropes and MAP or SBP before starting inotropes are more important factors for predicting the 28-day mortality in the PICU than the use of inotropes

There are some limitations of this study. This study was a retrospective single-center study, investigating only HSCT patients. Thus, the results cannot be generalized to all hemato-oncologic patients. It is necessary to study larger cohorts of HSCT patients from multiple centers. In conclusion, this study investigated the patients admitted to the PICU after HSCT at a single center. We found that the number of HSCTs received, use of MV, and the severity of illness scores (OPRISM-III, PRISM-III, and pSOFA scores) were the strong prognostic factors for PICU mortality in the critically-ill pediatric patients after HSCT.

CONFLICT OF INTEREST

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

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Can the intensivists predict the outcomes of critically ill patients on the appropriateness of intensive care unit admission for limited intensive care unit resources ?

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The coronavirus disease 2019 (COVID-19) pandemic continues to affect countries throughout the world. Since the first case of COVID-19 was announced in China in January 2020, the disease has spread rapidly, becoming a pandemic, with 259,465,151 infected and 5,174,661 deaths worldwide as of November 2021.

In South Korea, 4,116 new COVID-19 cases were reported on November 24, 2021, raising the total caseload to 425,065, according to the Korea Disease Control and Prevention Agency. This marked the highest number since the country reported its first confirmed case of COVID-19 in January 2020. The number of critically ill patients hit an all-time high of 586. The country added 35 more deaths from COVID-19, the highest number since the start of the fourth wave of the pandemic in July. The death toll has now reached 3,363, with the fatality rate standing at 0.79% as the number of critically ill patients is on the rise.

As the global COVID-19 pandemic persisted, problems such as limited medical resources, insufficient intensive care unit (ICU) equipment, and medical staff shortages gradually intensified. In particular, medical shortages may make it difficult to achieve timely hospitalization and adequate intensive care such as mechanical ventilation. Thus, there is a need for appropriate hospitalization and risk identification strategies for patients who are disproportionately likely to experience critical complications or mortality.

In these clinical situations, intensivists have a core role and responsibility to provide prognostic guidance, which is an essential part of shared decision-making [1] that requires integrating prognostic assessments with patients' values and preferences [2]. Previous studies have shown that ICU physicians are moderately accurate in predicting in-hospital mortality [3,4], but evaluations of ICU physicians' abilities to predict longer-term mortality and functional outcomes have been limited to patients who require long-term mechanical ventilation [5].

In this issue of *Acute and Critical Care*, Chang et al. [6] reported the outcomes of patients perceived as non-beneficially or beneficially admitted to the ICU and evaluated whether their prognosis was consistent with the intensivists' perceptions. This study found that the perceptions of the intensivists of the appropriateness of ICU admission were consistent with the prognosis of critically ill patients. Intensivists' perceptions were identified as a significant predictor of not only ICU outcomes (short-term prognosis) but also 6-month outcomes (long-term prognosis). The survival rate at the time of ICU discharge between the non-beneficial

Editorial

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and beneficial admission groups was significantly different (36% vs. 78%), and it further diverged at the 6-month follow-up (0% vs. 52%).

The authors concluded that the outcomes of patients perceived as having non-beneficial ICU admissions were extremely poor. The intensivists' perceptions were important in predicting patients' outcomes and were more consistent with the long-term prognosis than with immediate outcomes. Therefore, intensivists should play a role in determining how to utilize limited ICU resources.

The numerous extant clinical scoring systems for critically ill patients, such as Acute Physiology And Chronic Health Evaluation (APACHE), Sequential Organ Failure Assessment (SOFA), and Simplified Acute Physiology Score (SAPS), provide information on the short-term mortality rate but have limitations in predicting the patient's long-term prognosis and quality of life [7-9]. This gap underscores the importance of the role played by critical care physicians or intensivists.

Furthermore, in this study, when intensivists judged the futility of ICU admission based on their expertise, their perceptions were found to be in good agreement with both the short-term and long-term prognoses. These results suggest the possibility that intensivists' perceptions can supplement and compensate for the limitations of current scoring systems for critically ill patients.

Of course, there is no single method to predict the prognosis of ICU patients and to resolve the issue of futile ICU care. However, through a combination of diverse clinical parameters, scoring systems, and intensivists' perceptions, we will arrive at better and more efficient solutions for resolving these limitations. Future studies should also focus on improving the allocation of scarce ICU resources during the COVID-19 pandemic.

CONFLICT OF INTEREST

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

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The first case of abdominal mycotic aneurysm caused by K1 hypervirulent *Klebsiella pneumoniae* in a healthy adult

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Incidence of hypervirulent *Klebsiella pneumoniae* (hvKp) infection has been steadily increasing in the Asia-Pacific rim. The characteristic of hvKp infection is its ability to cause multiple site infections and unpredictable metastatic spread in the community. We describe the first case of mycotic aneurysm caused by hvKp serotype K1 in a previously healthy man and review the literature. Of a total of 13 cases, including our case, three cases were related to hvKp. Among patients with hvKp, the level of mycotic aneurysm in most patients was the infrarenal aorta, and they underwent an aortic graft or coil embolization. All strains were susceptible to most antimicrobial agents, except ampicillin. Early detection of hvKp can help to prevent the metastatic spread of pathogens and be useful for optimal patient care and epidemiologic research.

Key Words: hypervirulent; infected aneurysm; *Klebsiella pneumoniae*; liver abscess; metastatic infection

Case Report

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The prevalence of *Klebsiella pneumoniae* colonization rate in healthy adults range from 20% to 87% in Asian countries [1-3]. In particular, hypervirulent *K. pneumoniae* (hvKp) with a hypermucoviscous phenotype has recently been increasing in the community [1,4]. The hvKp has an ability to infect healthy individuals of any age and can infect any part of the body [5]. Liver abscess in the absence of biliary tract disease is a hallmark of the clinical syndrome. These patients have pneumonia, necrotizing fasciitis, endophthalmitis, prostatic abscess, and meningitis [3,6]. In addition, they are more likely to have diabetes mellitus (DM) and are at risk of life-threatening diseases even in healthy conditions [6]. Although extrahepatic complications from bacteremic dissemination have been observed, infected aneurysms are rare. Herein, we report a case of hvKp (serotype K1) causing liver abscess, septic emboli in both lungs, renal abscess, and prostate abscess, followed by an abdominal mycotic aneurysm that was not discovered at the initial presentation time in a previously healthy man. We further review the literature on the clinical characteristics of mycotic aneurysms caused by *K. pneumoniae* reported worldwide.

CASE REPORT

A previously healthy 50-year-old man was admitted on July 29, 2020, with a headache and

fever which had lasted for a week. His body temperature was 39.3°C, blood pressure was 106/65 mm Hg, pulse rate was 80 beats/min, and he was mentally alert. We suspected acute meningitis of the sudden and persistent severe headache with fever that has not been previously. A lumbar puncture was performed, but pleocytosis was not observed. Laboratory findings revealed a white blood cell count of 19,200/μl (reference range, 4,000–10,000), a C-reactive protein level of 36.1 mg/dl (reference range, 0.0–0.3), an erythrocyte sedimentation rate of 120 mm/hr (reference range, 0–20), an alkaline phosphatase level of 1,284 IU/L (reference range, 104–338), an alanine aminotransaminase of 29 IU/L (reference range, 4–44), an aspartate aminotransferase of 47 IU/L (reference range, 8–38), and a serum creatinine level which was within the normal range. The multifocal abscesses in the liver (Figure 1A), lung, kidney, and prostate was seen on enhanced abdominal computed tomography (CT). Piperacillin/tazobactam was administered as an empirical antibiotic agent. Ultrasound-guided percutaneous drainage of the liver was performed, and a yellowish fluid was drained. The patient was diagnosed with DM (glycated hemoglobin, 9.8%) on admission. *K. pneumoniae* with susceptibility to all antibiotics except ampicillin was isolated from blood and liver abscess culture (BACT/ALERT 3D system; bioMérieux, Marcy-l'Étoile, France) on August 2, 2020 (Table 1). The cultures were incubated for 24–48 hours, inoculated onto blood agar, and colonies were collected from the plates for identification using an automated system (VITEK II, bioMérieux). The antibiotic agent was changed to ciprofloxacin, which has a definite narrow spectrum on August 2, 2020. There were no abnormal findings on ophthalmological examination, brain magnetic resonance imaging, and transthoracic echocardiography. After antibiotic administration and liver abscess aspiration, bacteremia and inflammation marker were improved. However intermittent up to 38°C of fever has been continued. Although liver abscess and metastatic infections improved on follow-up CT on the 11th day of hospitaliza-

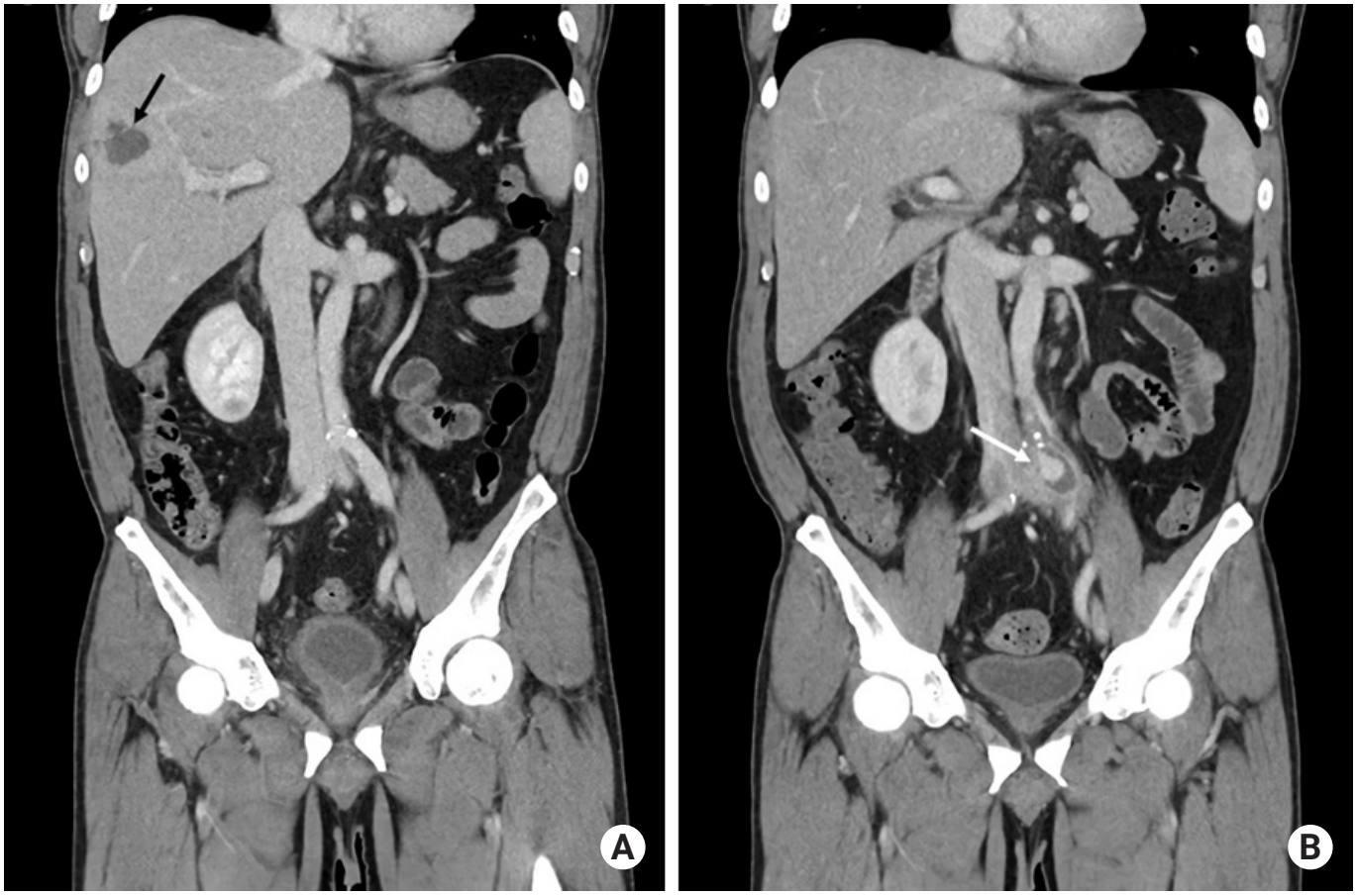

Figure 1. (A) Low-density lesion in the liver (black arrow) and (B) new aneurysmal dilatation with thrombosis, wall enhancement, and periarterial fatty infiltration in left common iliac artery (white arrow) are observed using enhanced abdominal computed tomography.

Table 1. Antibiotic susceptibility of *Klebsiella pneumoniae* isolated from blood and liver abscess

Antibiotic agent	MIC (μg/ml)	Interpretation
Amoxicillin plus clavulanic acid	≤2	S
Amikacin	≤2	S
Aztreonam	≤1	S
Ciprofloxacin	≤0.25	S
Ertapenem	≤0.5	S
Imipenem	≤0.25	S
Cefotaxime	≤1	S
Cefepime	≤1	S
Piperacillin plus tazobactam	≤4	S

MIC: minimum inhibitory concentration; S: susceptible.

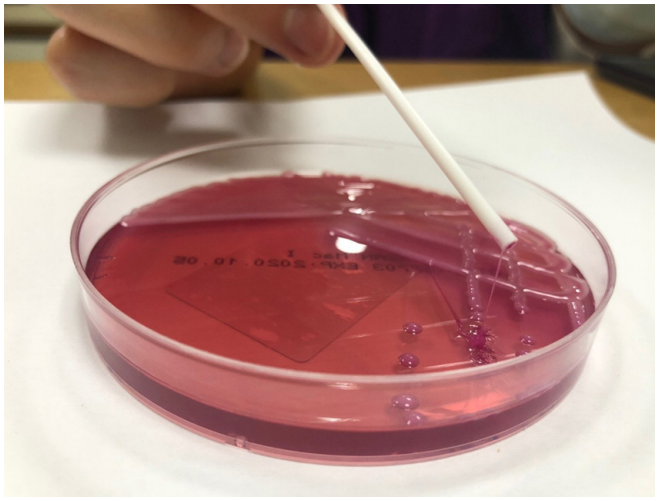

Figure 2. String test is used to confirm the hypermucoviscosity of *Klebsiella pneumoniae* isolates recovered from the blood culture. A positive result was defined as the formation of a viscous rope of length >5 mm when a bacterial colony was touched with a loop on the agar plate.

tion, a mycotic aneurysm developed in the left common iliac artery (Figure 1B). *K. pneumoniae* isolates with hypermucoviscosity phenotype were recovered from the string test of colonies obtained from the blood culture and pus from the liver abscess (Figure 2). The K1 serotype was identified by 16S rRNA gene analysis. The patient underwent left common iliac artery resection and repair with a Dacron graft performed on a 2.7 cm pseudoaneurysm in the abdominal aorta on the 15th hospital day. He was treated with a 6-week course of antibiotic treatment and recovered well.

DISCUSSION

K. pneumoniae is a common pathogen that causes urinary tract infection, intra-abdominal infection, and pneumonia in the community [7]. It also causes multidrug resistance in healthcare-associated infections. In addition, the emergence of severe community onset of hvKp has been increasing in East Asia since 1980, and more recently worldwide, mainly by serotypes K1 and K2. Clonal groups 23 are associated with the highly serum-resistant K1 capsule and a number of virulence factors [4,7]. However, there are a few reports of infected aortic aneurysms caused by classical *K. pneumoniae*, and those caused by hvKP are extremely rare. Because the mortality of mycotic aneurysms remains high, and hvKp is a very rapidly progressing infectious disease, close monitoring and evaluation of the clinical condition and imaging might be needed. Surgical intervention and appropriate antibiotic treatment are indispensable for reducing mortality rates.

This is the first case of a mycotic aneurysm caused by the hvKP serotype K1. The patient was previously healthy, except for newly diagnosed DM. In addition, he showed rapidly progressive multifocal abscesses. Despite adequate antibiotic therapy and drainage, an additional mycotic aneurysm developed. It is likely that it is not easy to control the progress of the disease with only appropriate antibiotic treatment in the early phase of hvKP. The K1 structure might confer increased resistance to a group of hvKp in which the hypermucoviscous phenotype capsule protects the cell from external factors (complement, anti-microbial peptides). It may also interfere with the function of other surface-located proteins to form biofilms [8].

The pathophysiology of mycotic aneurysms consists of bacteremia with septic emboli and subsequent arterial wall invasion, local proliferation of adjacent infectious lesions, and pathogens lodging in pre-existing aortic aneurysms in patients with predisposing factors such as hypertension and diabetes mellitus. Mycotic aneurysms caused by gram-positive cocci were significantly more likely to occur in the suprarenal arteries. Gram-negative bacilli causing mycotic aneurysms developed in patients receiving steroid treatment and in those with DM [3]. However, although this patient was newly diagnosed with DM, he did not have any other predisposing factors. No atherosclerotic lesion was found on the resected aorta.

A PubMed review of the literature published between 1980 and August 2020 was performed using a combination of terms, including "mycotic aneurysm," "aortitis," and "*Klebsiella*." A total of 12 cases in 10 articles were identified, which reported mycotic aneurysm and aortitis caused by *K. pneumoniae*.

Table 2. Clinical characteristics of patients with mycotic aneurysm caused by *Klebsiella pneumoniae* in worldwide

Case no.	Year	Age (yr)	Gender	Country	Medical Hx	Symptom	Level of MA	Other infection site	String test	Serotype	Genotype	Op	Outcome
1	2020	50	M	KR	DM	Fever, headache	Left common iliac artery	Liver, lung, kidney, prostate	P	K1	NA	Aortic graft	Improved
2	2011	47	M	TW	HTN	Fever, dyspnea	Aortic arch to suprarenal aorta	None	NA	NA	NA	Aortic graft	Died
3	2016	81	M	JP	None	Vision loss	Left internal iliac artery	Liver, brain, prostate	P	NA	*magA* *rmpS*	Coil	Improved
4	2018	63	M	KR	None	Abdominal pain	Infrarenal aorta	None	NA	NA	NA	Aortic graft	Improved
5	2008	48	M	TW	DM	Abdominal pain	Infrarenal aorta	None	NA	K5	*rmpA* iuc	Aortic graft	Improved
6	2005	70	M	JP	lymphoma	Fever	Distal aortic arch	None	NA	NA	NA	Aortic graft	Improved
7	2005	75	M	JP	DM, myositis[a]	Fever, back pain	Suprarenal aorta	None	NA	NA	NA	Aortic graft	Improved
8	2005	82	M	JP	DM, CVA	Fever	Distal aortic arch	None	NA	NA	NA	Aortic graft	Improved
9	1996	68	M	TW	DM	Lower back pain, fever	Suprarenal aorta	None	NA	NA	NA	Refuse[b]	Died
10	1996	NA	M	JP	DM	NA	Right internal iliac artery	None	NA	NA	NA	Excision and bypass	Improved
11	2004	67	M	USA	DM, CKD, CAD	abdominal pain, fever	Infrarenal aorta[c]	Psoas muscle	NA	NA	NA	Resection of the infected aorta	Improved
12	2005	68	F	TW	DM	NA	Thoracic and abdominal aorta	None	NA	NA	NA	Surgical intervention	NA
13	2008	69	M	KR	DM	back pain, fever	Infrarenal aorta	Endophthalmitis	NA	NA	NA	Aortic graft	Vision loss

Hx: history; MA: mycotic aneurysm; Op: operation; KR: South Korea; DM: diabetes mellitus; P: positive; NA: not applicable; TW: Taiwan; HTN: hypertension; JP: Japan; KR: Korea; CVA: cerebral vascular accident; USA: United States of America; CKD: chronic kidney disease; CAD: coronary artery disease.
[a]He had taken prednisolone for *rmpS* in the lower part of left lower extremity; [b]An emergency operation was suggested, but the family refused any surgical procedure; [c]He had a ruptured abdominal aortic aneurysm.

This amounts to a total of 13 cases, including the current case. Three cases were associated with hvKP (one serotype K1 in Korea in 2020 [this case], one virulent factor *magA*, *rmpS* in Japan in 2016 [9], and one serotype K5 in Taiwan in 2008 [10]). The main clinical features of these patients are shown in Table 2. The clinical presentation symptoms were not specific. All patients required imaging like computer tomography for diagnosis. They improved after antibiotic treatment and surgical treatment. Most patients were men. Two patients died. All strains were generally highly susceptible to antimicrobial agents, except for ampicillin. Antibiotic susceptibility has not changed over the last four decades worldwide. In the three hvKp cases, the patients had diabetes or received steroids; two cases had multiple abscesses including a liver abscess, and one case was a primary mycotic aneurysm without a liver abscess. The patients' levels of mycotic aneurysm were the infrarenal aorta, and they underwent aortic graft or coil embolization.

In conclusion, to the best of our knowledge, this is the first documented report worldwide of a mycotic aneurysm with multiple disseminated abscesses, including a liver abscess caused by serotype K1 *K. pneumoniae*. HvKp causes a metastatic infectious lesion from an early phase of the clinical course. Even with proper treatment, it did not improve. In particular, vascular complications of hvKp are associated with poor prognosis, and long-term treatment is inevitable owing to the difficult surgical approach. Therefore, it would be helpful for good prognosis that hvKp is diagnosed early and managed actively through multidisciplinary treatment.

CONFLICT OF INTEREST

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

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Acute lung injury following occupational exposure to nitric acid

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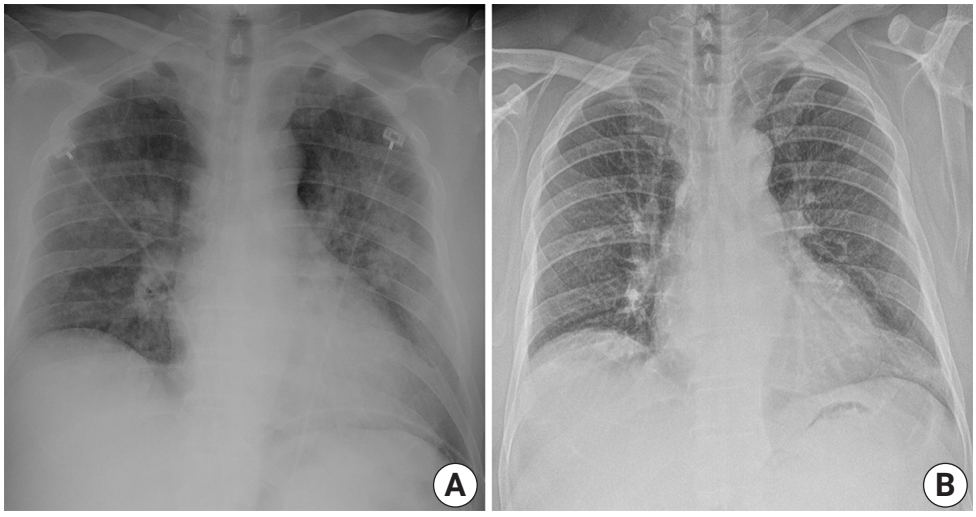

Figure 1. Chest radiograph. (A) Initial chest X-ray demonstrates diffuse bilateral opacities. (B) At hospital discharge, chest X-ray showed marked improvement.

Nitrogen dioxide is one of the compounds formed from breakdown of nitric acid and can lead to extensive damage to the pulmonary epithelium, causing both airway damage and inflammation [1-3]. A 60-year-old male presented to the emergency room complaining of deteriorating productive cough with dyspnea. The patient worked in a metal plating factory and reported 2-minute inhalation of nitric acid approximately 25 hours prior to arrival. At presentation, arterial blood gas analysis showed pH 7.37, partial pressure of carbon dioxide 41 mm Hg, and partial pressure of oxygen 59 mm Hg on 15 L/min of oxygen with a non-rebreathing mask. Crackles were audible over the posterior of both lungs. The chest X-ray showed diffuse bilateral opacities (Figure 1A), and computed tomography presented bilateral peribronchial consolidation and ground glass opacity with sparing in the subpleural region (Figure 2). The patient was treated with high-flow nasal oxygen therapy and transferred to an intensive care unit. Administration of bronchodilator and methylprednisolone (70 mg/day [1 mg/kg]) was initiated. He achieved clinical improvement and was transferred to the general ward with 5 L/min via nasal cannula. The patient was discharged 7 days after admission without oxygen

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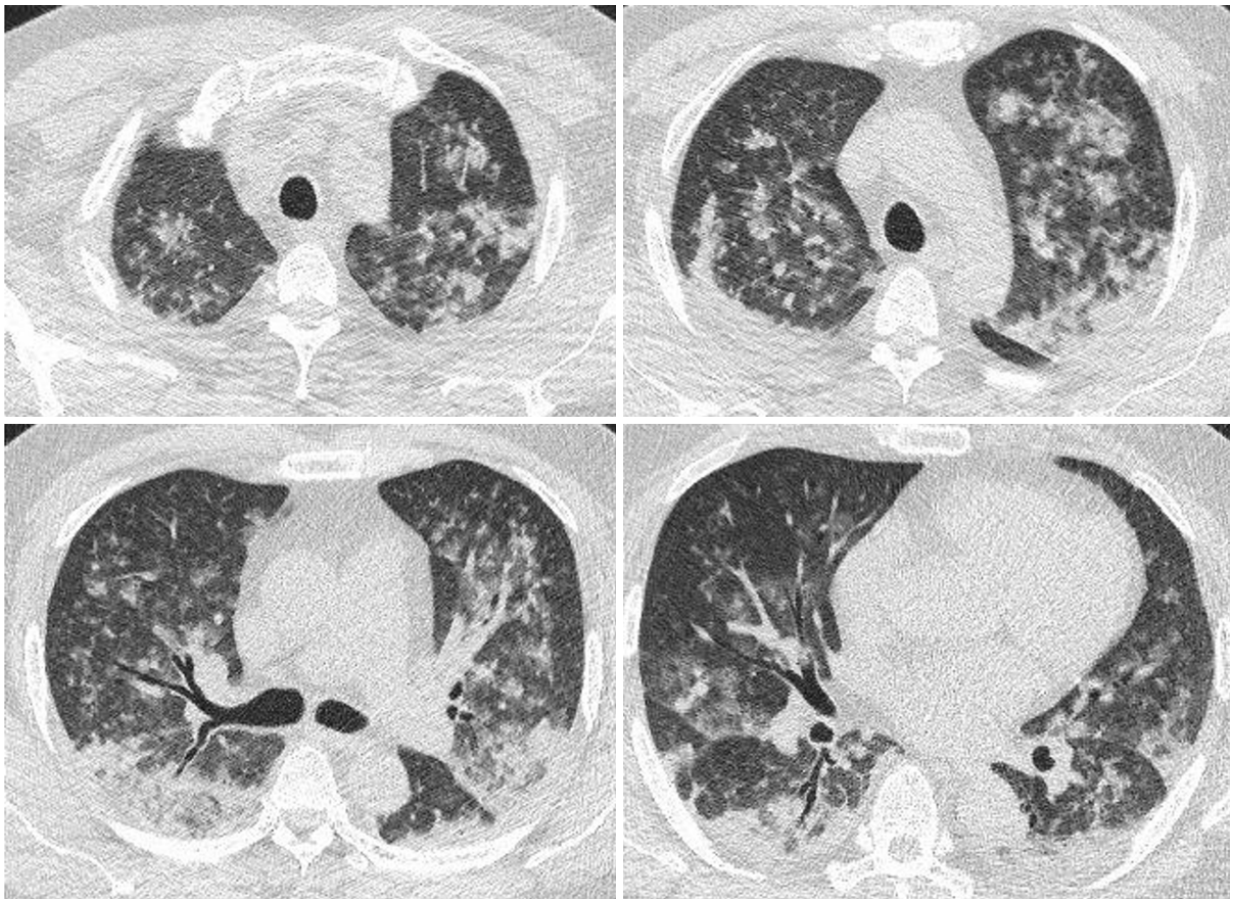

Figure 2. Chest computed tomography scan obtained on the day of emergency room visit presents bilateral peribronchial consolidation and ground glass opacity with sparing in the subpleural region.

therapy (Figure 1B). At discharge, methylprednisolone was reduced to 30 mg/day for 1 week and eventually discontinued after further reduction to 15 mg/day.

CONFLICT OF INTEREST

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

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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.

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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*. Place of publication: Publisher; Published year.

*Mark edition if it is beyond the 2nd edition.

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

C. Book Chapter

Authors of chapter. Title of chapter. In: Editors of book, editor(s). Title of book. Edition. Place of publication: 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. Philadelphia: 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]. Bethesda (MD): U.S. National Library of Medicine; 2000 [cited 2016 Nov 12]. Available from: https://clinicaltrials.gov/ct2/show/NCT02477618?term=NCT02477618&rank=1.

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