REFERENCES
2. Declining direct variable daily costs only.
3. A number of additional sensitivity analyses were performed, including one in which the total ICU costs were based on the cumulative sum of daily TISS points over the ICU period, and two further scenarios, with
4. The daily unit costs for these three consecutive ICU periods were set to decline toward discharge, reflecting the observed reduction in mean daily Therapeutic Intervention Scoring System (TISS)
5. The total ICU costs associated with each study sedative were calculated on the basis of total study sedative consumption and the number of days patients remained intubated, required non-invasive ventilation, or

1. Intensive Care Unit (ICU) Sedation
   - Initiation: 1 mcg/kg over 10 to 20 minutes.
   - Maintenance: 0.2 to 0.7 mcg/kg/hr. The rate of the maintenance infusion should be adjusted to achieve the desired level of sedation.
2. Procedural Sedation
3. Study design
   - The objective of the study was to evaluate the net effect of dexmedetomidine on total ICU costs and to compare it to sedation with propofol or midazolam (or per cohort, a 1:1 mix of both, annually) in ICU patients requiring
4. Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the
5. Sedation • Initiation: 1 mcg/kg over 10 minutes. For less invasive procedures such as ophthalmic surgery, a loading • Maintenance: 0.6 mcg/kg/hr and titrated to achieve desired clinical effect with doses ranging from 0.2 to 1 mcg/kg/hr. A
6. Patients with decreased cardiac function. Patients with hypovolemia. Patients with hepatic impairment. Patients with renal impairment.
Aims and Scope
Acute and Critical Care (abbreviated as Acute Crit Care, ACC) is a peer-reviewed scientific journal that publishes current works and ideas in critical and intensive care medicine. It informs clinical and experimental results and evidences for all critical care physicians, critical care nurses, and other healthcare professionals and improves the care of critically ill patients. It is a medium dedicated to basic, experimental, translational research as well as clinical studies related to all fields of critical illness. It publishes journals quarterly. All or part of the Journal is indexed by Emerging Sources Citation Index (ESCI), PubMed, PubMed Central (PMC), Scopus, KCI (Korea Citation Index), K重中科, KCI (Korean Medical Citation Index), DOAJ (Directory of Open Access Journals), EBSCO, CrossRef, Google Scholar, ScienceCentral, and the Journal can also be downloaded from the homepage of the Korean Society of Critical Care Medicine (http://www.ksccm.org) and the Journal's web site (http://accjournal.org or http://acuteandcriticalcare.org).

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

Ownership
Acute and Critical Care (abbreviated as Acute Crit Care) is the official publication of the Korean Society of Critical Care Medicine (KSCCM), which was founded in 1980. (http://eng.ksccm.org/html/?pmode=history)

Title change and language
In 2018, the name of the official publication of KSCCM was changed from Korean Journal of Critical Care Medicine (1986 – 2017) to Acute and Critical Care (Acute Crit Care, ACC, 2018 – ). Articles were written in Korean and English until 2013. From 2014, articles were published exclusively in English. (http://eng.ksccm.org/html/?pmode=history)

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# Contents

## Guideline

2021 KSCCM clinical practice guidelines for pain, agitation, delirium, immobility, and sleep disturbance in the intensive care unit  
Yijun Seo, Hak-Jae Lee, Eun Jin Ha, Tae Sun Ha  

## Review Articles

Awakening in extracorporeal membrane oxygenation as a bridge to lung transplantation  
Su Hwan Lee  

Brain-lung interaction: a vicious cycle in traumatic brain injury  
Ariana Alejandra Chacón-Aponte, Érika Andrea Durán-Vargas, Jaime Adolfo Artévalo-Carrillo, Iván David Lozada-Martínez, María Paz Bolaño-Romero, Luis Rafael Moscote-Salazar, Pedro Grille, Tariq Janjua  

## Original Articles

A machine learning model for predicting favorable outcome in severe traumatic brain injury patients after 6 months  
Mehdi Nourelahi, Fardad Dadboud, Hossein Khalili, Amin Niahan, Hossein Parsaei  

Association between the National Health Insurance coverage benefit extension policy and clinical outcomes of ventilated patients: a retrospective study  
Wanho Yoo, Saerom Kim, Soohan Kim, Eunsuk Jeong, Kwangha Lee  

Nosocomial meningitis in intensive care: a 10-year retrospective study and literature review  
Sofia R. Valdoleiros, Cristina Torrão, Laura S. Freitas, Diana Maria, Celina Gonçalves, Carla Teixeira  

Comparison of high-flow nasal oxygen therapy and noninvasive ventilation in COVID-19 patients: a systematic review and meta-analysis  
Glenardi, Febie Christiyya, Bambang J Oetoro, Ghea Mangkuliguna, Natalia  

Clinical characteristics and outcomes of critically ill COVID-19 patients in Sfax, Tunisia  
Mabrouk Bahloul, Sana Kharrat, Kamilla Chtra, Malek Hafghi, Olfa Turki, Najeh Baccouche, Rania Ammar, Nazha Kallel, Majdi Hsairi, Olfa Chakroun-Walha, Chokri Ben Hamida, Hedi Chelly, Khaireddine Ben Mahfoudh, Abielhamid Karoui, Hela Karray, Nouredine Rekik, Mounir Bouaziz  

Diaphragm ultrasound as a better predictor of successful extubation from mechanical ventilation than rapid shallow breathing index  
Mohammad Jhahidul Alam, Simanta Roy, Mohammad Azmain Iktidar, Fahmida Khatun Padma, Khairul Islam Nipun, Sreetha Chowdhury, Ranjan Kumar Nath, Harun-Or Rashid
## Contents

<table>
<thead>
<tr>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>The feasibility and safety of percutaneous dilatational tracheostomy without endotracheal guidance in the intensive care unit</td>
<td>101</td>
</tr>
<tr>
<td>Ji Eun Kim, Dong Hyun Lee</td>
<td></td>
</tr>
<tr>
<td>Serum lactate levels in cirrhosis and non-cirrhosis patients with septic shock</td>
<td>108</td>
</tr>
<tr>
<td>Surat Tongyoo, Kamonlawat Sutthishop, Tanuwong Viarasilpa, Chairat Permpikul</td>
<td></td>
</tr>
<tr>
<td><strong>Editorial</strong></td>
<td></td>
</tr>
<tr>
<td>The effect of socioeconomic status, insurance status, and insurance coverage benefits on mortality in critically ill patients admitted to the intensive care unit</td>
<td>118</td>
</tr>
<tr>
<td>Moo Suk Park</td>
<td></td>
</tr>
<tr>
<td><strong>Case Report</strong></td>
<td></td>
</tr>
<tr>
<td>Successful noninvasive ventilation in a severely acidotic and hypercapnic comatose COVID-19 patient with multiple comorbidities: a case report</td>
<td>120</td>
</tr>
<tr>
<td>Joseph Abraham Poonuraparampil, Habib Md Reazaul Karim, Manu P Kesavankutty, Porika Prashanth Nayak</td>
<td></td>
</tr>
<tr>
<td><strong>Letters to the Editor</strong></td>
<td></td>
</tr>
<tr>
<td>Neurological complications during the course of severe COVID-19: is it just the tip of the iceberg?</td>
<td>124</td>
</tr>
<tr>
<td>Gulcin Koc Yamanyar, Burcin Halaci, Mehmet Yildirim, Arzu Topeli</td>
<td></td>
</tr>
<tr>
<td>Inhaled iloprost can improve oxygenation and shunt fraction in severe COVID-19</td>
<td>127</td>
</tr>
<tr>
<td>Christiaan M.C. Serbanescu-Kele Apor de Zalán, Norbert A. Foudraine, Jos L.M.L. Le Noble</td>
<td></td>
</tr>
<tr>
<td>Gravity-induced ischemia in the brain-and prone positioning for COVID-19 patients breathing spontaneously</td>
<td>131</td>
</tr>
<tr>
<td>J. Howard Jaster, Giulia Ottoviani</td>
<td></td>
</tr>
<tr>
<td>Gravity-induced ischemia in the brain and prone positioning for COVID-19 patients breathing spontaneously: still far from the truth!</td>
<td>134</td>
</tr>
<tr>
<td>Mabrouk Bahloul, Sana Kharrat, Kamila Chtara, Hedi Chelly, Chokri Ben Hamida, Mounir Bouaziz</td>
<td></td>
</tr>
</tbody>
</table>
2021 KSCCM clinical practice guidelines for pain, agitation, delirium, immobility, and sleep disturbance in the intensive care unit

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We revised and expanded the “2010 Guideline for the Use of Sedatives and Analgesics in the Adult Intensive Care Unit (ICU).” We revised the 2010 Guideline based mainly on the 2018 “Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption (PADIS) in Adult Patients in the ICU,” which was an updated 2013 pain, agitation, and delirium guideline with the inclusion of two additional topics (rehabilitation/mobility and sleep). Since it was not possible to hold face-to-face meetings of panels due to the coronavirus disease 2019 (COVID-19) pandemic, all discussions took place via virtual conference platforms and e-mail with the participation of all panelists. All authors drafted the recommendations, and all panelists discussed and revised the recommendations several times. The quality of evidence for each recommendation was classified as high (level A), moderate (level B), or low/very low (level C), and all panelists voted on the quality level of each recommendation. The participating panelists had no conflicts of interest on related topics. The development of this guideline was independent of any industry funding. The Pain, Agitation/Sedation, Delirium, Immobility (rehabilitation/mobilization), and Sleep Disturbance panels issued 42 recommendations (level A, 6; level B, 18; and level C, 18). The 2021 clinical practice guideline provides up-to-date information on how to prevent and manage pain, agitation/sedation, delirium, immobility, and sleep disturbance in adult ICU patients. We believe that these guidelines can provide an integrated method for clinicians to manage PADIS in adult ICU patients.

Key Words: agitation; delirium; guideline; pain; rehabilitation; sleep

INTRODUCTION

Critically ill adult patients treated in an intensive care unit (ICU) are exposed to an unpleasant environment, with uncontrolled light and noise. They experience moderate to severe pain at rest, as well as during general care procedures (such as mechanical ventilation and invasive procedures, nursing care, and trauma or comorbidity-induced pain). Severe pain can induce various stress responses in critically ill patients and lead to agitation, sleep disturbance, and delirium. A deep level of sedation and delirium is related to detrimental clinical...
outcomes such as longer ICU length of stay (LOS), a longer duration of mechanical ventilation, and increased mortality. Therefore, a multidisciplinary strategy, including optimizing pain management, maintaining light sedation, performing routine monitoring and treatment for delirium, providing active rehabilitation in the ICU, and treating sleep disturbance using a sleep-promoting protocol, needs to be implemented to improve clinical outcomes of critically ill ICU patients. Furthermore, the appropriate administration of medications for pain, sedation, and delirium has varied among clinicians. Improper pharmacologic interventions might be associated with negative outcomes in critically ill adult patients.

The Standardization Committee in the Korean Society of Critical Care Medicine (KSCCM) developed the “2010 Guideline for the Use of Sedatives and Analgesics in the Adult Intensive Care Unit” to assist clinicians with the provision of adequate treatment for pain and sedation in the ICU. Since the 2010 guideline was published, there have been significant advances in the therapeutic approach and management for pain, agitation, and delirium (PAD) in critically ill ICU patients. In addition, as our knowledge has expanded, we have come to understand that rehabilitation/mobilization may be beneficial for delirium treatment, and that sleep is a modifiable risk factor influencing the recovery of critically ill patients.

Herein, we report recommendations regarding how to prevent and manage pain, agitation/sedation, delirium, immobility, and sleep disturbance in critically ill ICU patients by updating the “2010 Guideline for the Use of Sedatives and Analgesics in the Adult Intensive Care Unit.”

MATERIALS AND METHODS

Selection of Panel Members
Board members of the KSCCM appointed an editor for the revision and update of the “2010 Guideline for the Use of Sedatives and Analgesics in the Adult Intensive Care Unit.” The panel members of the Guideline Committee were recruited from the members of the KSCCM. The KSCCM approved all panelists. The panelists included two surgeons, a neurosurgeon, and an anesthesiologist, and all panelists were intensivists. None of the panelists had any conflicts of interest with the related topic.

Guideline Development
The 2010 guidelines were not published in a specific journal, but were released as a booklet during the 30th KSCCM Annual Congress and posted on the KSCCM homepage. We revised the “2010 Guideline for the Use of Sedatives and Analgesics in the Adult Intensive Care Unit” based mainly on the 2018 “Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption (PADIS) in Adult Patients in the ICU,” which was an updated 2013 PAD guideline with the inclusion of two additional topics (rehabilitation/mobility and sleep). Because it was not possible to hold face-to-face meetings of the panels due to the coronavirus disease 2019 (COVID-19) pandemic, all discussions took place via virtual conference platforms and e-mail with the participation of all panelists. All authors drafted the recommendations, and all panelists discussed and revised the recommendations several times. All panelists voted on the quality level of each recommendation, and each recommendation was required to have at least 75% agreement with a 100% response rate of the entire panel to be included in the final guideline. The development of this guideline was independent of any industry funding.

Assessing Quality of Evidence
The quality of evidence for each recommendation was ranked as high (level A), moderate (level B), or low/very low (level C) based on both study design and specific study characteristics that could prompt a reviewer to either downgrade or upgrade the quality of the evidence. The levels were defined as follows. Level A: Scientific evidence provided by well-designed, well conducted, controlled trials (randomized or nonrandomized) with statistically significant results that consistently support
the recommendation of the guideline; Level B: Scientific evidence provided by observational studies or by controlled trials with less consistent results to support the recommendation of the guideline; Level C: Although expert opinion supports the recommendation of the guideline, scientific evidence provides inconsistent results, or such evidence is lacking.

**Peer Review**
External reviewers who were not involved in the development of the guideline reviewed it before it was published. The final manuscript was reviewed and approved by the Board of the KSCCM.

**RESULTS**

**Pain**
According to the definition of the International Association for the Study of Pain, pain is an unpleasant sensory and/or emotional experience related to real or potential tissue injury [1]. Pain management is complicated because pain is highly individual. It can arise from diverse origins, including neuropathic, visceral, and somatic causes. Each patient has subjective perceptions of pain with a different degree of endurance. Critically ill patients in the ICU experience moderate to severe pain not only from standard care procedures, but also at rest. Severe pain can induce stress responses such as tachycardia, increased oxygen consumption in the myocardium, hypercoagulation, respiratory compromise, immunosuppression, and increased catabolism, leading to tissue perfusion disorders and reduced tissue oxygen partial pressure. Thus, appropriate pain control in ICU patients is indispensable. The implementation of assessment-driven and standardized pain management is vital due to the characteristics of critically ill patients, such as communication disorders, altered mental status, mechanical ventilation, invasive procedure and devices, and immobility. Compared to conventional treatment, protocol-based pain control and sedation may reduce nosocomial infections, hypotension, bradycardia, the use of sedatives without increased narcotic analgesics, the duration of mechanical ventilation, ICU LOS, and severity of pain [2,3]. Thus, it is recommended to regularly conduct a protocol-driven pain assessment using validated tools and provide a definite guideline for medication selection and dosage. In addition, step-by-step pain management that prioritizes pain control prior to the administration of sedatives is recommended.

**Risk factors**

**KSCCM Recommendation**
- All adult ICU patients have the right to receive adequate analgesia and pain management. (grade A)

ICU patients commonly complain of moderate to severe pain and physical discomfort even at rest due to various factors, such as one or more comorbidities, regular nursing care, invasive procedures, and various injuries [4]. Psychological factors, such as anxiety and depression, and demographic and clinical factors such as young age, various comorbidities, and operation history can influence pain at rest [5]. In particular, procedures frequently performed in critically ill adults, including insertion of an arterial catheter, removal of the chest tube and wound drain, position change and turning, and endotracheal suction, are associated with the greatest increases in pain intensity. Pain severity before treatment, the procedure type, diagnosed traumatic and surgical injuries, and demographic characteristics, including young age, female sex, and non-Caucasian race, influence the intensity of pain during a procedure. Inadequate pain treatment causes sleep deprivation, exhaustion, and disorientation, as well as agitation, which is often observed in ICU patients [6].

**Assessment**

**KSCCM Recommendation**
- We recommend that clinicians should perform routine and reproducible pain assessments and evaluate responses to pain treatment using the patient’s self-report or Behavioral Pain Scales (BPS). (Grade B) [Update]
- A patient’s self-report of pain intensity is a reference standard for evaluation and treatment of pain. The 0–10 Numeric Rating Scale (NRS) is recommended for pain assessment. (Grade B)
- The most reliable tools for pain assessment in adult ICU patients who cannot self-report are the BPS and the Critical-Care Pain Observation Tool (CPOT). (Grade B) [Update]

For patients who can communicate, the most reliable and appropriate method of pain assessment is self-reporting. The assessment of pain should consider the characteristics of pain such as site, feature, aggravating or alleviating factors, and intensity. The 0–10 NRS is a scale in which the patient selects the intensity of pain from 0 to 10 corresponding to their pain,
with a score of 3 or less indicating adequate pain control and a score of 10 indicating the worst pain. The 0–10 NRS (in verbal or visual format) for adult ICU patients who can self-report is an effective and feasible method [7].

The Verbal Descriptor Scale (VDS) is a descriptive pain assessment scale using a series of descriptive phrases referring to different levels of pain intensity, with a horizontal line of 10 cm indicating “no pain,” “very severe pain,” or “extremely severe pain” at each end. It may be applied in ICU patients who cannot use a numeric assessment scale such as the 0–10 NRS. In one study, ICU patients undergoing cardiac surgery stated that the 0–10 NRS or VDS was superior to the visual analog scale in identifying pain intensity and preferred to use the VDS for pain assessment [8]. The 0–10 Faces Pain Scale, which was validated in 105 postoperative cardiac surgery ICU patients, is easy to use and useful for identifying pain intensity and shows a good correlation with the VDS (Figure 1) [9].

Critically ill ICU patients often become unable to express pain intensity while receiving sedatives, anesthetics, neuromuscular blockers, and mechanical ventilation. In critically ill adults who cannot self-report pain with observable behaviors, the BPS and CPOT demonstrate the greatest validity and reliability for monitoring pain (Tables 1 and 2) [10,11]. When a patient cannot self-report, the family can participate in the patient’s pain assessment, and family-reported pain has been shown to be closer to the patient’s self-report than the reports of attending nurses and physicians [12]. However, the degree of agreement between the family and the patient for pain intensity is moderate. Compared with seriously ill patients’ self-reports, surrogates tended to overestimate pain intensity. Thus, family participation in pain assessment cannot replace the role of attending nurses and physicians [13]. Vital signs including heart rate, blood pressure, respiratory rate, oxygen saturation, and end-tidal CO₂ are not reliable parameters for pain monitoring and assessment in adult ICU patients. They can be considered as a signal to begin a further evaluation using reliable and adequate tools, including a patient’s self-report or behavioral scale (BPS and CPOT) [14].

Table 1. Description of the Behavior Pain Scale [10]

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facial expression</td>
<td>Relaxed</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Partially tightened (e.g., brow lowering)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Fully tightened (e.g., eyelid closing)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Grimacing</td>
<td>4</td>
</tr>
<tr>
<td>Upper limbs movement</td>
<td>No movement</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Partially bent</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Fully bent with finger flexion</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Permanently retracted</td>
<td>4</td>
</tr>
<tr>
<td>Compliance with ventilation</td>
<td>Tolerating movement</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Coughing, but tolerating ventilator for the most of time</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Fighting ventilator</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Unable to control ventilation</td>
<td>4</td>
</tr>
</tbody>
</table>

Figure 1. Various pain assessment scales: Numeric Rating Scale (NRS), Verbal Descriptor Scale (VDS), and Faces Pain Scale (FPS).
Choice of analgesia

The selection of appropriate analgesia should be preceded by nonpharmacologic therapy that can maintain patients’ comfort through a proper body posture, fixation of fractures, and removal of other physical stimuli. Nonpharmacologic therapy can reduce the unnecessary use of analgesia and maximize the effect of analgesia. Other nonpharmacologic interventions to reduce pain include massage, cold therapy, and relaxation therapy. However, their level of evidence supporting their recommendation is low.

Various pain-modulating medications such as opioids, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and anticonvulsants can be used to manage pain in adult ICU patients (Figure 2). To select an optimal analgesic and its dosage suitable for individual patients, the drug’s pharmacologic properties and adverse effects should be considered. Local analgesia, volatile anesthetics, NSAID gels, and non-opioid drugs or NSAIDs, whether intravenous (IV) or orally administered, are not recommended for use before an ICU procedure to avoid pain originating from the procedure.
Seo Y, et al. 2021 KSCCM PADIS guidelines in adult ICU

Opioids

KSCCM Recommendation

- We recommend that the treatment plan and the goal of optimal pain management should be determined individually or personalized and that all participating clinicians should share this information for consistent analgesic therapy. (Grade C)

- If continuous IV administration of opioids is required, fentanyl, hydromorphone, and remifentanil are recommended. (Grade C) [Update]

IV opioids are the most important treatment for non-neuropathic pain in adult ICU patients. Opioids act on several central and peripheral opium receptors to mediate the analgesic effect. Among those receptors, μ and κ receptors are the most important. The activities of these two receptors and other receptors are related to side effects. The prerequisite conditions for ideal opioid therapy include rapid onset of action, easy dose titration, no accumulation of the drug or its metabolites in the body, and low cost. Commonly used opioids in adult ICU patients include morphine, morphine, hydromorphone, and remifentanil. In particular, remifentanil has the advantages of rapid onset/offset action and safety regardless of liver and kidney dysfunction. Thus, remifentanil can be applied through continuous IV administration in patients requiring frequent awakening (Table 3) [16].

Non-opioid analgesics

KSCCM Recommendation

- A “multi-modal analgesia” strategy is likely to reduce opioid consumption with improved pain-modulating effects, pain control, and patient-centered outcomes.

Table 3. Pharmacologic actions of opioid analgesics

<table>
<thead>
<tr>
<th>Opioids (route)</th>
<th>Equianalgesic dose</th>
<th>Onset</th>
<th>Elimination half-life</th>
<th>Intermittent dosing</th>
<th>IV infusion rate</th>
<th>Side effect and other information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine (IV)</td>
<td>10 mg</td>
<td>5–10 min</td>
<td>3–4 hr</td>
<td>2–4 mg q1-2 hr</td>
<td>2–30 mg/hr</td>
<td>Accumulation in patients with liver dysfunction</td>
</tr>
<tr>
<td>Hydromorphone (IV)</td>
<td>1.5 mg</td>
<td>5–15 min</td>
<td>2–3 hr</td>
<td>0.2–0.6 mg q1-2 hr</td>
<td>0.5–3 mg/hr</td>
<td>Accumulation in patients with kidney and liver dysfunction</td>
</tr>
<tr>
<td>Fentanyl (IV)</td>
<td>100 μg</td>
<td>1–2 min</td>
<td>2–4 hr</td>
<td>0.35–0.5 μg q 0.5–1 hr</td>
<td>0.7–10 μg/kg/hr</td>
<td>Accumulation in patients with kidney and liver dysfunction, release of histamine</td>
</tr>
<tr>
<td>Remifentanil (IV)</td>
<td>1–3 min</td>
<td>3–10 min</td>
<td>Loading dose: 1.5 μg/kg Available regardless of liver and kidney dysfunction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maintenance dose: 0.5–15 μg/kg/hr</td>
<td></td>
<td></td>
<td></td>
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</table>

IV: intravenous.

(Grade C) [Update]

- NSAIDs, acetaminophen, and nefopam can be used as adjunctive opioid analgesics in critically ill adults. (Grade C) [Update]

- Gabapentin, carbamazepine, and pregabalin can be used with an opioid for neuropathic pain management. (Grade A) [Update]

- Low-dose ketamine can be used as an adjunct to an opioid for pain management. (Grade C) [Update]

IV opioids are the mainstay of pain treatment in most ICUs. However, their adverse effects, including sedation, delirium, respiratory depression, and ileus, might prolong the ICU LOS and aggravate post-ICU patient results. A “multi-modal analgesia” strategy is needed to reduce opioid use and increase the pain-modulating effects, improving pain control and patient-centered outcomes [17]. Non-opioid analgesics are able used as adjunctive painkillers to decrease the dosing of opioids. Their use should be adjusted according to each patient’s conditions and symptoms to reduce the risk (Table 4).

Few NSAIDs have analgesic effects similar to those of opioids. Ketorolac (a non-COX-1-specific NSAID) is currently the only NSAID approved for IV use as an alternative to opioids for pain management. The analgesic effect of ketorolac after intramuscular (IM) injection begins to appear at 1 hour, reaching its maximum effect at 2 hours. It lasts 5 to 6 hours. A single 30-mg dose of IM ketorolac shows an equivalent effect to a single 4-mg dose of IV morphine. Although ketorolac can be used as a single agent, its administration together with opioids can reduce the opioid dose by 25%–50%. Acetaminophen and nefopam can be used as adjunctive analgesics in critically ill patients to reduce opioid use and improve analgesic effectiveness [18]. Nefopam exerts an analgesic effect by inhibiting
dopamine, noradrenaline, and serotonin reuptake. A 20-mg dose shows an equivalent effect to a 6-mg dose of IV morphine [19]. Ketamine can improve pain relief and reduce opioid requirements by reducing hyperalgesia at doses lower than an anesthetic dose. An adjunctive dose of ketamine is common at a 0.1–0.5 mg/kg IV bolus followed by a 1–2 μg/kg/min continuous IV infusion. For neuropathic pain management in critically ill patients, neuropathic analgesics such as gabapentin, carbamazepine, and pregabalin should be used with an opioid [20]. Lidocaine and COX-1-selective NSAIDs should not be used routinely as adjuncts to opioids for pain management in adult ICU patients.

Methods of dosing analgesics

**KSCCM Recommendation**

- Continuous IV infusion or an intermittent scheduled-administration strategy of analgesics is more useful for retaining consistent analgesic action than administration upon patient demand. (Grade B)
- A patient-controlled analgesia (PCA) device helps administer opioids to patients who can understand and handle the device. (Grade B)
- Fentanyl or remifentanil for rapid pain management is useful for patients with acute conditions. (Grade C) [Update]
- Fentanyl, hydromorphone, or remifentanil is useful for patients with hemodynamic instability or renal failure. (Grade C) [Update]

- It is recommended to use morphine and hydromorphone with longer durations of action if a patient inevitably needs intermittent boluses. (Grade C)

In principle, analgesics should be administered as a continuous IV infusion unless there is a particular reason not to do so. A continuous IV infusion can maintain a constant blood concentration and avoid drug toxicity since a lower dose is administered at one time than in a single bolus administration. In addition, IV administration has the advantage of making it possible to adjust the blood concentration according to the infusion rate. As an alternative option, PCA, which refers to a system when an analgesic is administered upon the patient’s need, has the disadvantage of administering a smaller dose than the prescribed dose, which can cause a severe delay in pain management [21]. Daily awakening of patients from analgesics and sedation can effectively manage pain intensity, reduce total opioid consumption, and shorten the ICU LOS and the duration of mechanical ventilation [22]. PCA used in non-critical patients shows a stable drug concentration, high-quality analgesia, less sedation, reduced opioid consumption, and low incidence of respiratory complications compared to other opioid administration strategies. When considering PCA, clinicians should pay attention to the patient’s consciousness, hemodynamic reservoir, and history of opioid abuse [23]. A transdermal fentanyl patch is useful for long-term analgesia in hemodynamically stable patients, as it can release the drug uniformly, although the degree of absorp-
tion varies according to permeability, body temperature, tissue perfusion, and skin thickness. The maximal blood concentration differs significantly between patients. Since a fentanyl patch takes 12 to 24 hours to reach maximal effectiveness, it is not recommended for rapid pain control. Moreover, it takes a similar amount of time for the drug effect to disappear after removing the patch.

Adverse effects of analgesics

**KSCCM Recommendation**

- Opioids should be used cautiously due to respiratory depression, opioid-induced hypotension, and reduced bowel motility. (Grade C)
- Ketorolac administration should be used for up to 5 days. Clinicians should carefully monitor for possible renal failure and gastrointestinal bleeding. (Grade C)
- IV acetaminophen should be used cautiously due to IV acetaminophen-associated hypotension, which can occur in up to 50% of patients. (Grade C) [Update]

**Opioids**

The side effects of opioid analgesics are respiratory depression, effects on the cardiovascular system, and changes in bowel motility. Opioids can cause a dose-dependent decrease in the respiratory rate and tidal volume. They can also reduce blood pressure and the heart rate by inhibiting the sympathetic nervous system and enhancing the parasympathetic nervous system. However, opioid-induced hypotension responds well to fluid therapy or vasopressors in most cases. Naloxone at 4 to 8 mg can antagonize the decreased bowel motility caused by opioids without antagonizing the analgesic effect. A small dose of naloxone (0.25 to 1 μg/kg/hr) can control opioid-induced pruritis that does not respond to an antihistamine without antagonizing the analgesic effect. Opioids can stimulate chemical receptors in the vomiting center of the brainstem, thus inducing vomiting. All opioids have the same degree of emetogenic effect. However, if one drug causes vomiting, switching to another drug can sometimes improve symptoms. Serotonin antagonists and low-dose opioid antagonists can also help relieve symptoms. Opioids can increase muscle tone and evoke muscle rigidity in severe cases. Regarding the mechanism, opioids act on the spinal cord or supraspinal level of the central nervous system, not directly on the muscle [24]. Severe muscle rigidity can induce a decrease in lung elasticity and a decline of functional residual capacity of the lung, leading to ventilation impairment [25]. Non-depolarizing muscle relaxants can reduce the severity of muscle rigidity. Thiopental and low-dose diazepam or midazolam can decrease and prevent muscle rigidity [26].

**Non-opioid analgesics**

Non-opioid analgesics occasionally cause gastrointestinal bleeding or surgical wound bleeding and suppress renal function by interfering with prostaglandin synthesis in the kidneys. NSAID-associated renal injuries frequently occur in patients with hypovolemic status, renal hypoperfusion due to old age, and renal dysfunction. In addition, ketorolac use for over 5 days more than doubles the risk of renal toxicity and bleeding. When acetaminophen is administered through the IV route, hypotension (a reduction in mean arterial pressure >15 mm Hg) may occur in up to 50% of patients [27]. Nefopam should be used selectively due to its association with tachycardia, glaucoma, seizure, and delirium. The side effects of ketamine include nausea, delirium, hallucination, hypoventilation, pruritus, and sedation, and have an incidence similar to that of opioid side effects.

**Agitation/Sedation**

In critically ill patients, sedatives are frequently administered to relieve anxiety, reduce the stress of dependence on mechanical ventilation, and control agitation [28]. Agitation can cause difficulties with mechanical ventilation, hypoxia due to increased oxygen consumption, barotrauma, hypotension, accidental removal of instruments or catheters, and in-hospital infections. However, sedatives can increase patients’ morbidity. Thus, specific reasons are required to use them. Patients’ sedation status must be frequently reassessed using valid and reliable scales while using sedatives [29,30].

**Goals for the sedation level**

**KSCCM Recommendation**

- Clinicians should establish a sedation level and time to discontinue sedatives in each patient and regularly adjust those targets. (Grade C)
- The sedative dose can be titrated to maintain a light rather than a deep level of sedation in critically ill patients on mechanical ventilation unless clinically necessary. (Grade B) [Update]
- A light level of sedation can be achieved and maintained using daily sedation interruption (DSI) and a nurse-protocolized targeted sedation protocol. (Grade C) [Update]
An appropriate sedation level depends on the patient’s disease course and treatment regimen. Since the prognosis is poor when deep sedation occurs in the ICU, other than in exceptional cases, a light sedation state wherein the patient can be easily awakened while maintaining a normal sleep-wake cycle is desired rather than deep sedation. Although there is no consensus on the definition of the depth of sedation (light, moderate, or deep), light sedation usually ranges from −1 to −2 on the Richmond Agitation-Sedation Scale (RASS) [22]. However, a RASS score in the −2 to +1 range has also been considered light sedation in a few studies [30]. Maintaining light sedation shortens the weaning time, reduces the frequency of tracheostomy, and shortens the ICU LOS. Contrary to the 2013 guidelines, however, the maintenance of light sedation does not reduce 90-day mortality, delirium, post-traumatic stress disorder, or depression or increase unplanned self-extubation [31,32]. In critically ill intubated adult patients, a light level of sedation can be achieved and maintained using DSI and nurse-protocolized targeted sedation protocol (NP-targeted sedation). DSI attempts to help patients arouse and be weaned from mechanical ventilation. NP-targeted sedation is a sedation protocol applied by nurses who adjust drug concentration at the bedside to achieve target sedation scores [33,34].

Sedatives can relieve patients’ stress and help facilitate general procedures in the ICU. They are essential for the treatment process of critically ill patients, as they can dramatically help maintain patients’ safety and comfort. However, to prevent side effects caused by excessive use, patients’ sedation levels should be assessed. After an assessment, continuous dosing is recommended whenever possible to achieve an appropriate level of sedation. If necessary, intermittent dosing may be used. The target sedation level should be determined at the start of treatment depending on the patient’s condition. It should be evaluated and adjusted again from time to time. Consideration should be given to writing sedative prescriptions in such a way that the daily sedative requirement may be adjusted up and down.

Assessment of the sedation level

**KSCCM Recommendation**

- We recommend using the RASS and Sedation-Agitation Scale (SAS) to assess the degree and level of sedation. (Grade B) [Update]
- Sedation monitoring based on the bispectral index (BIS) rather than a subjective scale may facilitate titration of sedation when a sedation assessment scale cannot be used due to deep sleep or muscle relaxants. (Grade C) [Update]

There are various sedation assessment tools, including the RASS, Ramsay scale, Riker SAS, Motor Activity Assessment Scale (MAAS), and Observer Assessment of Alertness/Sedation (OAA/S) scale (Table 5) [35]. Among them, the RASS and SAS are widely used to assess the degree and depth of sedation in ICU patients. The SAS was the first sedation level assessment method with confirmed reliability. It consists of seven items describing patient behavior [36]. The RASS is a tool that evaluates arousal state, cognitive function, and response sustainability based on a score of −5 to +4. It is the most effective and stable sedation assessment tool, along with the SAS [37]. The MAAS is a modified version of the SAS. It consists of seven categories of patient behavior. Its reliability has been verified as a method of evaluating the sedation level of critically ill patients [38]. The OAA/S scale indicates the degree of response to pinching or calling a name on a scale of 0 to 5. It is known to have significant sensitivity to the degree of sedation [22].

Objective sedation monitoring is useful when a patient’s behavior cannot be observed due to deep sedation or therapeutic muscle relaxants. Methods for objectively measuring brain function include auditory evoked potentials, the BIS, the patient state index, and state entropy. These methods are not recommended for critically ill patients who are not unconscious or paralyzed. However, recent studies have shown that using BIS may have a potential effect on patients with light sedation, such as reducing the need for tracheostomy, treatment-related side effects, total sedative and fentanyl doses, and shortening the ICU stay [39,40]. Vital signs are not specific or sensitive for assessing the sedation level.

**Sedatives**

The medications used for sedation include benzodiazepines, propofol, central α2-agonists, and other agents (Table 6). Indications, goals, clinical pharmacology, and cost of sedatives are important determinants when selecting sedatives.

**Benzodiazepines**

Benzodiazepines can cause anterograde amnesia, which interferes with the memory of unpleasant experiences that occur after drug use. They do not cause retrograde amnesia. They have an anticonvulsant effect without an analgesic action. Nonetheless, they can lower the expected pain response. Thus, the analgesic dose can be reduced when benzodiazepines are used together with analgesics [41]. Their main indications are sedative treatment and short-term use for anxiety, panic disorder, alcohol withdrawal, preoperative anxiety, initial treatment
of convulsions, muscle spasms, and insomnia. Benzodiazepine drugs have many differences in efficacy, onset, duration of action, metabolism, and the presence of active intermediates. The intensity and duration of effects may vary depending on age, underlying diseases, past alcohol abuse history, medication history, and other factors. Thus, the appropriate dose may vary. In elderly patients, the clearance of benzodiazepines (and their intermediate metabolites) is slow, or benzodiazepines have a larger volume of distribution. Thus, the drug clearance time may be significantly longer in elderly patients than in younger patients [42]. Liver failure or renal insufficiency can also slow drug clearance [43]. In case of a benzodiazepine overdose, flumazenil can be used as an antagonist to reverse its excessive sedative and hypnotic effects. A dose of 0.3–2.0 mg should be administered in divided IV injections [44]. However, its use is not recommended because it may increase withdrawal symptoms and myocardial oxygen consumption. When testing for continuous sedation, it is recommended to use a single shot at a low dose.

Benzodiazepines include midazolam, lorazepam, and diazepam. Midazolam is effective for acute excitatory patients because of its rapid onset time. However, it has been reported that its sedative effect continues to appear in critically ill patients with obesity, low serum albumin, or renal failure [45,46]. Its long-term sedative effects can also occur due to the accumulation of active metabolites such as α-hydroxymidazolam,

### Table 5. Scales used to measure sedation and agitation [35]

<table>
<thead>
<tr>
<th>Score</th>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Combative</td>
<td>Violent, immediate danger to staff</td>
</tr>
<tr>
<td>3</td>
<td>Very agitated</td>
<td>Pulls at or removes tubes, aggressive</td>
</tr>
<tr>
<td>2</td>
<td>Agitated</td>
<td>Frequent non-purposeful movements, fights ventilator</td>
</tr>
<tr>
<td>1</td>
<td>Restless</td>
<td>Anxious, apprehensive but movements not aggressive or vigorous</td>
</tr>
<tr>
<td>0</td>
<td>Alert &amp; calm</td>
<td>Not fully alert, sustained awakening to voice (eye opening &amp; contact &gt;10 sec)</td>
</tr>
<tr>
<td>−1</td>
<td>Drowsy</td>
<td>Briefly awakens to voice (eye opening &amp; contact &lt;10 sec)</td>
</tr>
<tr>
<td>−2</td>
<td>Light sedation</td>
<td>Movement or eye-opening to voice (no eye contact)</td>
</tr>
<tr>
<td>−3</td>
<td>Moderate sedation</td>
<td>No response to voice, but movement or eye opening to physical stimulation</td>
</tr>
<tr>
<td>−4</td>
<td>Deep sedation</td>
<td>No response to voice or physical stimulation</td>
</tr>
<tr>
<td>−5</td>
<td>Unrousable</td>
<td>No response to verbal or physical stimulation</td>
</tr>
</tbody>
</table>

### Table 6. Pharmacologic actions of sedative medications

<table>
<thead>
<tr>
<th>Sedative</th>
<th>Onset</th>
<th>Elimination half-life</th>
<th>Active metabolite</th>
<th>Intermittent dosing</th>
<th>IV infusion rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>2–5 min</td>
<td>3–11 hr</td>
<td>Yes (prolonged sedation, especially with renal failure)</td>
<td>0.01–0.05 mg/kg over several minutes</td>
<td>0.02–0.1 mg/kg/hr</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>10–40 min</td>
<td>8–15 hr</td>
<td>None</td>
<td>0.02–0.04 mg/kg (≤2 mg)</td>
<td>0.02–0.06 mg/kg q 2–6 hr prn or 0.01–0.1 mg/kg/hr (≤10 mg/hr)</td>
</tr>
<tr>
<td>Diazepam</td>
<td>2–5 min</td>
<td>20–120 hr</td>
<td>Yes (prolonged sedation)</td>
<td>5–10 mg</td>
<td>0.03–0.1 mg/kg q 0.5–6 hr prn</td>
</tr>
<tr>
<td>Propofol</td>
<td>1–2 min</td>
<td>Short-term use: 3–12 hr</td>
<td>Yes (prolonged sedation)</td>
<td>5 μg/kg/min over 5 minutes</td>
<td>5–50 μg/kg/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Long-term use: 50x.18.6 hr</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>5–10 min</td>
<td>1.8–3.1 hr</td>
<td>None</td>
<td>1 μg/kg/min over 10 minutes</td>
<td>0.2–0.7 μg/kg/hr</td>
</tr>
</tbody>
</table>

IV: intravenous; prn: pro re nata.
especially in patients with renal failure [46]. The metabolism of midazolam is significantly inhibited by propofol, diltiazem, macrolide antibiotics, and other cytochromes P450 isoenzyme 3A4 antagonists, prolonging the duration of its drug action [43]. Midazolam has high level of fat solubility. It can act very quickly and produce a sedative effect within 2–5 minutes of an IV bolus injection. However, it is not possible to induce a normal sleep pattern. Continuous IV administration of midazolam can cause excessive sedation due to its accumulation in tissues. Thus, it is recommended to limit the administration of midazolam to within 48 hours. With daily awakening, drug interruption, and dose re-optimization according to the RASS, it is possible to reduce the drug demand and shorten the length of ventilation and ICU stay [47]. Lorazepam has a slow onset of action, making it difficult to use in patients with acute anxiety. It has a long half-life of 12–15 hours, making it difficult to quickly optimize the dose during continuous infusion. Nonetheless, it has few interactions with other drugs and sedation can be maintained by intermittent administration or continuous infusion. The initial loading dose should be administered through an IV push of a set dose. It should be diluted to a concentration of 1 mg/ml or less. Precipitation may occur despite these precautions. When lorazepam is administered at a high dose, polyethylene glycol and propylene glycol (PG) as solvents are known to cause acute reversible renal tubular necrosis, lactic acidosis, and a hyperosmolar state. PG toxicity refers to significant accumulation of PG when the difference in osmotic pressure before and after lorazepam administration is 10–12 mOsm/L or more. Diazepam provides a rapid onset of sedation and rapid awakening when it is administered as a single dose. Since its metabolite has a long-term effect, the sedation state can be sustained during repeated administration. Thus, diazepam can be used for long-term sedative treatment.

**Propofol**

Propofol is administered through IV injections for general anesthesia and sedation. It has sedative, sleep-inducing, anti-anxiety, memory loss, antiemetic, and anticonvulsant effects. However, it has no analgesic effect. It can reduce cerebral blood flow and brain metabolism. It can also lower intracranial pressure more effectively than fentanyl in cases of severe brain injury. It is used as a sedative in patients with elevated intracranial pressure. No pharmacokinetic changes have been reported in patients with renal or hepatic failure. Due to its high fat solubility, propofol can quickly cross the blood-brain barrier, leading to rapid sedation. Its sedative effect is lost quickly after short-term use due to its rapid redistribution and high liver and extrahepatic clearance. Because its sedative effect dissipates quickly, temporary discontinuation during infusion allows a neurological evaluation, which is advantageous when frequent waking for neurological examinations is required or when performing a daily waking protocol. However, there are reports showing that awakening is delayed after 12 hours of infusion [48]. Thus, caution is needed. Propofol can induce injection site pain, bradycardia, respiratory depression, and dose-dependent hypotension due to systemic vasodilation, which occurs more frequently when it is administered with other sedatives and analgesics or when it is used in patients with preexisting respiratory failure and cardiovascular instability. Since long-chain triglycerides have a caloric value of 1.1 kcal/ml, long-chain triglycerides used as a drug carrier should be included in the total calories provided to the patient at an amount corresponding to the administered drug. Long-term or high-dose use may cause hypertriglyceridemia [49]. It should be noted that when propofol is administered, propofol infusion syndrome (PRIS) can occur with an incidence of 1%, resulting in the exacerbation of metabolic acidosis, hypertriglyceridemia, hypotension, arrhythmias, acute renal failure, hyperkalemia, rhabdomyolysis, and hepatic dysfunction. In adults, PRIS is related to high-dose administration of more than 70 μg/kg/min. It can also occur with a low-dose continuous IV infusion. The mortality rate of PRIS is as high as 33%. It may not improve even if continuous dosing is stopped [50]. To prevent PRIS, it is recommended to substitute propofol with other sedatives for 24 hours every 5 days. Propofol does not mix well with other drugs, and it can be a source of infection. Thus, a dedicated catheter should be used for continuous infusion. Among the existing propofol formulations, Diprivan (AstraZeneca) contains edetic acid. If an IV infusion is continued for more than a week, a drug holiday is recommended to prevent abnormalities in trace elements. For other long-chain triglyceride propofol formulations, it is recommended that one injection period does not exceed 12 hours and that the mixed solution should be used within 6 hours after preparation.

**Dexmedetomidine**

A central α2-agonist, clonidine has been used to enhance the efficacy of opioid analgesics and general anesthetics, as well as to treat drug withdrawal syndrome. Dexmedetomidine is a more selective α2-agonist and has sedative, analgesic, and sympathetic suppression effects. However, it has no anticonvulsant effect. Dexmedetomidine causes less respiratory de-
pression than other sedatives. On electroencephalography, the sleep pattern induced by dexmedetomidine is similar to that of normal physiological sleep. Dexmedetomidine can induce cooperative sedation from which it is easy to awaken patients even during drug injection. It enables communication and command obedience. The onset of action is within 15 minutes of continuous infusion. The strongest sedative effect is induced within 1 hour. Administration of a loading dose may shorten the onset of action, but may lead to hemodynamic instability in severely ill patients. Dexmedetomidine does not have a significant effect on respiratory depression. Thus, it can be used in patients who have not been intubated. It can be given through the IV route after extubation. However, it is necessary to continuously monitor the respiratory system for hypoventilation and hypoxic partial pressure because dexmedetomidine can cause airway obstruction in patients who are not intubated through loss of muscle tone in the oropharynx.

**Choice of sedatives**

**KSCCM Recommendation**

- Propofol is useful in patients requiring rapid and frequent awakening for neurologic evaluations or extubation. (Grade B)
- Midazolam use is recommended for shorter time periods because when it is used for more than 48 to 72 hours, it becomes difficult to predict the recovery time or time for extubation. (Grade A)
- It is recommended to use propofol rather than benzodiazepines as a sedative in post-cardiac surgery adults on mechanical ventilation. (Grade C) [Update]
- Propofol and dexmedetomidine are recommended as sedatives rather than benzodiazepines in mechanically ventilated medical and surgical patients not undergoing cardiac surgery. (Grade C) However, benzodiazepines are recommended for alcohol withdrawal syndrome. [Update]
- Systematically applied reduction or adjustment of the sedative dose to reach the daily goal of sedation level is recommended to avoid unnecessary long-term sedation. (Grade A)
- Serum triglyceride concentrations should be monitored starting two days after propofol administration, and the fat calories in the emulsion should be included in the total calories. (Grade B)
- It is recommended to make and use an appropriate sedative administration guideline and treatment flow chart or protocol for the ICU. (Grade B)

Because elective cardiac surgery patients are often hospitalized urgently, the duration of stay in the ICU and mechanical ventilation are different from those of internal medicine or other surgical intensive care patients. Therefore, this guideline divides patients requiring mechanical ventilation into cardiac surgery and medical/surgical critical patients. The 2013 PAD guidelines stated that propofol or dexmedetomidine were favored over benzodiazepine sedatives such as midazolam and lorazepam because of more favorable short-term prognostic outcomes, such as the length of ICU stay and ventilation, as well the improvement of delirium symptoms [28]. In this guideline, the short-term prognosis (time to weaning from mechanical ventilation, time to light sedation), delirium, and the long-term prognosis (90-day mortality, cognitive and physical function, and psychological dysfunction) were evaluated.

It is recommended to use propofol rather than benzodiazepines as a sedative in adults who are mechanically ventilated after cardiac surgery. In comparison to benzodiazepines, propofol can shorten the average light sedation induction time by 52 minutes and the time to extubation of the endotracheal tube by 100 minutes on average [51-53].

We compared (1) propofol versus benzodiazepines, (2) dexmedetomidine versus benzodiazepines, and (3) propofol versus dexmedetomidine in medical and surgical patients who did not undergo cardiac surgery. In comparison to benzodiazepines, propofol shortened the induction time of shallow sedation by an average of 7.2 hours and the time to extubation of the endotracheal tube by an average of 11.6 hours [54,55]. However, the delirium incidence showed no difference between the two sedatives [56]. In randomized controlled trials (RCTs) comparing benzodiazepines and dexmedetomidine, dexmedetomidine reduced the time to extubation of the endotracheal tube by an average of 1.9 days, shortened the duration of mechanical ventilation, and significantly reduced the incidence of delirium [57,58]. However, dexmedetomidine and benzodiazepines did not show any significant differences in the duration of endotracheal extubation, LOS in the ICU, or the risk of delirium in an integrated analysis. Although the dexmedetomidine group showed frequent bradycardia, no intervention was needed in most cases [58].

There were no significant differences of the time to endotracheal extubation, bradycardia, or hypotension between propofol and dexmedetomidine. However, when dexmedetomidine was used, the occurrence of delirium was reduced and patients were able to communicate more easily [58].
Since neither propofol nor dexmedetomidine is superior, one of these two drugs is recommended as a sedative for critically ill adults. However, dexmedetomidine should not be used if a deep level of sedation with or without a muscle relaxant is needed. Figure 3 shows a pharmacologic treatment flowchart of agitation in mechanically ventilated patients. Benzodiazepines are recommended for alcohol withdrawal syndrome [59]. However, since the role of nonpharmacologic treatment for the reduction of anxiety, agitation, and psychologic distress is uncertain, sedatives are not recommended for alcohol withdrawal syndrome.

Discontinuation of sedatives

**KSCCM Recommendation**
- Benzodiazepine and propofol withdrawal symptoms are more likely to occur during high-dose treatment and if the patient has been infused for more than a week. These drugs should be systematically reduced to prevent withdrawal symptoms. (Grade B)

Patients taking analgesics or sedatives for more than a week may develop neurological changes or physiological dependence. Withdrawal symptoms may occur if analgesics or sedatives are abruptly discontinued. Benzodiazepine withdrawal symptoms and signs are myalgia, tremor, headache, nausea, diaphoresis, fatigue, anxiety, excitation, perceptual dysfunction, elevated sensitivity to light and sound, muscle spasms, myoclonus, sleep disturbances, delirium, and convulsions. Propofol withdrawal symptoms are similar to benzodiazepine withdrawal symptoms. High-risk patients for the development of withdrawal symptoms are those who have been admitted to the ICU for more than 7 days or have received lorazepam at doses higher than 35 mg/day [60,61]. In case of intermittent administration, switching to a long-acting drug is helpful in preventing withdrawal symptoms. After lowering the sustained infusion rate by 20%–40% for the first time, an additional 10% reduction every 12–24 hours depending on the patient’s response is also allowed to help reduce symptoms [61].

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**Figure 3.** Pharmacologic treatment flowchart for agitation in mechanically ventilated patients. IV: intravenous.
Physical restraints

**KSCCM Recommendation**
- Although physical restraints have various advantages, such as protecting staff from combative patients and preventing self-extubation, self-removal of medical devices, and falling accidents, a careful consideration of the advantages and disadvantages of physical restraints is recommended before initiation/maintenance of physical restraints. (Grade C) [Update]

Medical staff can consider using physical restraints to improve patient safety, protect staff from combative patients, prevent self-extubation, prevent self-removal of medical devices, prevent falling accidents, regulate patient behavior, and maintain patient posture/position [62,63]. Restraints usually fix the ankles, wrists, and upper body in place. However, in a few studies, the use of physical restraints was associated with a prolonged ICU stay, increased agitation, increased demand for opioids and sedatives, and risk of delirium or disorientation [64,65]. Risk factors that increase the use of physical restraints in critically ill adults include old age; non-comatose consciousness level; neurologic and psychologic status including delirium; sedative type, administration method, and dosing; mechanical ventilation; use of invasive devices; the nurse-to-patient ratio and perceived workload; and specific times of the day. Some patients who received physical restraints during their ICU stay have shown strong affective reactions even after transfer from the ICU to general ward [32]. Given the frequency of use of physical restraints, unintended consequences, and patient perceptions, health care providers should carefully consider the risks and effects before initiating/maintaining the use of restraints in an adult ICU.

Delirium

Delirium is defined as acute cerebral dysfunction accompanied by a change of level of consciousness, disorientation, and cognitive dysfunction during a short duration (hours to days). Delirium is classified into three subtypes: hyperactive (agitated), hypoactive (calm or lethargic), and mixed (fluctuation between the two subtypes). Among these three types, the mixed subtype occurs the most, and the hypoactive subtype has a worse prognosis. Approximately 20% to 80% of critically ill adult patients have experienced delirium during their ICU stay. Delirium is associated with increased ICU mortality, longer LOS in hospital, higher healthcare costs, and more long-term cognitive dysfunction, such as dementia. Thus, early recognition and treatment for delirium are essential [66,67]. Patients in whom delirium is detected early, followed by prompt treatment, show the same prognosis as patients who do not develop delirium.

**Risk factors**

Delirium occurrence, duration, and severity in adult ICU patients are strongly related to various risk factors (Table 7) [68]. Modifiable factors risk include benzodiazepine use and blood transfusion. Sex, opioid sedatives, mechanical ventilation, past history of pulmonary disease, hospital admission, nicotine use, dialysis, or continuous venovenous hemofiltration, and a lower Glasgow Coma Scale have been identified as having no relationship with an increased incidence of delirium.

The PREdiction of DELIRium in ICU patients (PRE-DELIRIC) model and early (E)-PRE-DELIRIC model can predict delirium in critically ill adult patients. The PRE-DELIRIC model consists of 10 predictors (age, Acute Physiology and Chronic Health Evaluation [APACHE] II score, admission group, emergent admission, infection, coma, sedation, morphine use, urea level, and metabolic acidosis). It can predict ICU delirium within 24 hours after ICU admission [69,70]. The E-PRE-DELIRIC model includes nine predictors (age, history of cognitive dysfunction, history of alcohol abuse, blood urea nitrogen, admission class, emergent admission, mean arterial blood pressure, use of steroids, and respiratory failure). It can predict ICU delirium at ICU admission [71].

**Assessment and outcomes**

**KSCCM Recommendation**
- Delirium in critically ill ICU patients should be monitored using the Confusion Assessment Method for the ICU (CAM-ICU) and intensive care delirium screening checklist (ICDSC) as valid tools. (Grade A)

<table>
<thead>
<tr>
<th>Table 7. Risk factors of delirium [68]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Use of benzodiazepines</strong></td>
</tr>
<tr>
<td>Transfusion</td>
</tr>
<tr>
<td>Increasing aging</td>
</tr>
<tr>
<td>Prior dementia</td>
</tr>
<tr>
<td>Pre-ICU emergency operation</td>
</tr>
<tr>
<td>Increasing APACHE and ASA scores</td>
</tr>
</tbody>
</table>

ICU: intensive care unit; APACHE: Acute Physiology and Chronic Health Evaluation; ASA: American Society of Anesthesiologists.
The early diagnosis of delirium can lead to rapid identification and correction of the cause or causes, relief of symptoms, pharmacologic or nonpharmacologic therapeutic interventions, and evaluation of treatment effectiveness. Thus, adult ICU patients should be routinely evaluated for delirium using a valid tool. The CAM-ICU and ICDSC are recommended as the most verified and reliable tools for delirium assessment in critically ill adult patients (Table 8) [72-74]. The level of consciousness of patients is checked using the RASS or SAS. Patients with a RASS score >–4 or SAS score >2 are eligible for delirium evaluation using the CAM-ICU (Figure 4). Ideally, clinicians should perform the CAM-ICU at least twice a day (day and night) to assess delirium. The CAM-ICU can even be used for delirium assessment in patients with speech impairment, endotracheal intubation, dementia, and severe depressive disorder. When evaluating delirium using the ICDSD, eight items derived from the Diagnostic and Statistical Manual of Mental Disorders criteria are identified over a 24-hour period. Four or more points on the ICDSC corresponds to a diagnosis of delirium.

A patient’s level of arousal may affect the assessment of delirium using verified screening tools. The diagnosis rate of delirium is significantly higher when patients have a RASS score of –2 compared to a RASS of –1 to 0. However, the effect of the level of arousal from sedatives on the evaluation of delirium needs further studies. Delirium is related to poor outcomes, even when accompanied by decreased arousal levels. Thus, clinicians should not underestimate the possibility and importance of delirium even in patients with decreased arousal levels. The occurrence of delirium in critically ill patients is closely related to cognitive dysfunction at 3 and 12 months after discharge from the ICU, and may be related to a prolonged hospital stay. It has been consistently shown that delirium in critically ill adult patients is not related to post-traumatic stress disorder or post-ICU distress. However, the outcomes of patients with rapidly reversible delirium are similar to those of patients who never experience delirium [75].

**Pharmacologic prevention and treatment**

**KSCCM Recommendation**

- Pharmacologic treatment for preventing delirium in critically ill patients is not recommended. (Grade B) [Update]
- Routine use of haloperidol, an atypical antipsychotic, a statin, or dexmedetomidine is not recommended for delirium treatment. However, treatment of delirium using these drugs can be considered if the symptoms of delirium may be harmful to patients. (Grade B) [Update]

Currently, the pharmacologic agents for delirium treatment include a typical antipsychotic (haloperidol), atypical antipsychotics (risperidone, olanzapine, quetiapine), and dexmedetomidine (Table 9).

**Pharmacologic treatment**

Routine use of haloperidol, atypical antipsychotics, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), or dexmedetomidine is not recommended for delirium treatment. In six RCTs, these drugs were not found to reduce delirium duration, shorten the ICU LOS, or diminish mortality [76-81]. However, short-duration use of haloperidol or an atypical antipsychotic may be helpful for patients who experience meaningful distress secondary to delirium symptoms, including agitation, panic, hallucination, and delusion, or who may be physically harmful to themselves or others due to anxiety. Atypical antipsychotics are preferred as they have a lower risk of extrapyramidal symptoms than haloperidol. However, atypical antipsychotics are not recommended for use in patients at risk of torsades de pointes (e.g., those with a prolonged QT interval on electrocardiography, administration of drugs that prolong the QT interval, or a history of arrhythmias). Dexmedetomidine use may be considered in patients with delirium on mechanical ventilation in whom agitation delays withdrawal/extubation of mechanical ventilation. Although benzodiazepines can induce delirium, they can be used in patients with secondary delirium related to alcohol or benzodiazepine withdrawal. The use of haloperidol or an atypical antipsychotic in critically ill patients with subsyndromal delirium is not associated with a reduced incidence of delirium or an improved prognosis [82].

**Pharmacologic prevention**

The use of haloperidol, atypical antipsychotics, statins, dexmedetomidine, and ketamine for delirium treatment is not recommended to prevent delirium in any adult ICU patients. Although a few studies reported that these drugs significantly reduced delirium incidence, their use is not associated with a reduced duration of mechanical ventilation, ICU LOS, or mortality. However, they can increase the risk of side effects. Thus, a nonpharmacologic prevention strategy is needed to decrease
Seo Y, et al. 2021 KSCCM PADIS guidelines in adult ICU

Acute and Critical Care 2022 February 37(1):1-25

Seo Y, et al. 2021 KSCCM PADIS guidelines in adult ICU

the incidence of delirium [83,84].

**Nonpharmacologic prevention and treatment**

**KSCCM Recommendation**

- We recommend a multicomponent (ABCDEF bundle) nonpharmacologic intervention strategy for the prevention and treatment of delirium. (Grade B) [Update]

A multicomponent, nonpharmacologic intervention that is focused on reducing modifiable risk factors for delirium, enhancing cognitive capability, and optimizing sleep, rehabilita-

tion/mobilization, hearing, and vision in critically ill patients is significantly associated with a lower incidence of delirium, a reduced duration of delirium, a decreased duration of mechanical ventilation, a shortened ICU LOS, and a lower risk of mortality [85-89]. Thus, clinicians should perform multi-component interventions to decrease or shortened the incidence and duration of delirium by performing reorientation, stimulating cognitive capability, using clocks, improving sleep quality by minimizing light and noise, minimizing sedation, reducing immobility through early rehabilitation and exercise, and decreasing hearing and/or visual impairment by using available devices including hearing aids or eyeglasses.
The bundle of awakening and breathing coordination, delirium monitoring/management, and early exercise/mobilization (ABCDE) meaningfully reduces the incidence of delirium. The increase in compliance with the ABCDEF bundle, which includes family participation (“F”), is significantly related to decreased mortality and prolongation of the period without coma or delirium in the ICU [80]. No studies have reported adverse effects from the application of multicomponent, non-pharmacologic intervention strategies.

Immobility (Rehabilitation/Mobilization)

KSCCM Recommendation
- As a vital component of critical care, the rehabilitation of critically ill patients is related to long-term outcomes. (Grade C) [Update]

In the past, the treatment of critically ill patients was focused on treating underlying internal/surgical problems by sedating patients and having them rest in bed. However, survivors of
Efficacy and benefits of rehabilitation

**KSCCM Recommendation**

- Rehabilitation in critically ill patients is related to a shortened duration of delirium, mechanical ventilation, and ICU LOS. (Grade C) [Update]

- Although rehabilitation interventions have no effect on mortality, continuous rehabilitation for critically ill patients can improve long-term survival. (Grade B)

Several RCTs have reported that intensive care rehabilitation treatment can strengthen limb and respiratory muscle strength, improve physical function and quality of life, shorten the duration of delirium and mechanical ventilation, and shorten the ICU LOS.

In a controlled study in which 60 patients were randomly assigned to a rehabilitation group and a control group, the duration of ventilation and the LOS in the ICU were shortened by 1.7 days and 2.5 days, respectively, in the rehabilitation group [95]. In a randomized controlled study of 90 patients, the rehabilitation group showed better results in the 6-minute walking distance test, quadriceps muscle strength test, and quality of life analysis (Physical Functioning Scale of the Short Form 36-item questionnaire) upon discharge from the hospital [96]. A meta-analysis of 43 RCTs also reported that rehabilitation decreased the duration of ventilation by 1.7 days and the ICU LOS by 1.2 days. However, it did not reduce the mortality rate. Many studies have similarly reported that intensive care rehabilitation does not reduce mortality [97].

The reason why rehabilitation treatment alone does not significantly affect mortality might be that many factors affect mortality. However, it has been reported that the proportion of 10-year survival was improved in patients who received rehabilitation treatment from the ICU even after discharge [98]. Based on this, it can be said that continuous rehabilitation treatment for critically ill patients can help improve their long-term survival rate.

Safety and risks of rehabilitation

**KSCCM Recommendation**

- Rehabilitation is an intervention that can be safely applied in the ICU. (Grade B) [Update]

- A rehabilitation program should consist of a rehabilitation protocol, safety and effectiveness index, and indications for stopping via a multidisciplinary approach according to the environment of each ICU. (Grade B) [Update]

Although the usefulness of rehabilitation for critically ill patients is recognized, the biggest stumbling block to its practical application is medical staff’s anxiety about patient safety. Critically ill patients have a variety of instruments such as a ventilator, central venous line, and arterial line, making it challenging to apply rehabilitation easily due to the risk of disconnection or accidental instrument removal and anxiety that a patient’s condition may worsen during rehabilitation associated with hemodynamic instability in critically ill patients.

However, many studies have reported that serious harm does not occur in intensive care rehabilitation. It has been reported that rehabilitation can be safely applied to those who are on ventilators and patients receiving continuous renal replacement therapy or extracorporeal membrane oxygenation [99,100].

In a prospective observational study with 1,100 patients and a total of 5,267 rehabilitation sessions, 34 (0.6%) adverse reactions occurred. The most common adverse reactions were arrhythmias (10 cases, 0.2%) and an increase in mean arterial pressure to 140 mm Hg or more (8 cases, 0.2%), which resulted in an increased LOS in the ICU. However, no serious adverse reactions were reported [101]. In a meta-analysis of 48 studies, only 78 cases (0.6%) out of a total of 14,398 rehabilitation sessions had adverse reactions. Very few adverse reactions may cause harm, such as falls and endotracheal tube dislocation [102].

It is important to set criteria for the implementation and discontinuation of rehabilitation treatment appropriate for the characteristics of each ICU and then implement the rehabilitation treatment accordingly (Table 10) [103]. Collaboration of various medical staff is essential for achieving this goal.
It is important that the ICU doctor, nurse, rehabilitation medicine doctor, and physical therapist form a team to develop a rehabilitation program tailored to the characteristics of each ICU. It is also necessary to develop a rehabilitation treatment program suitable for each hospital's situation by discussing the patients who will receive intensive care rehabilitation, evaluation indicators for safety and effectiveness, the rehabilitation protocol, and criteria for stopping treatment.

Sleep Disturbance

Causes

Sleep disturbance is one of the most common complaints of critically ill patients. Sleep disturbance in the ICU includes sleep segmentation, increased light sleep (N1+N2 stage), and decreased rapid eye movement (REM) sleep [104]. Sleep disturbance can cause delirium, prolong mechanical ventilation, and decrease immune function. Since sleep disturbance is a controllable risk factor for the development of delirium, the incidence of delirium can be lowered by correcting factors that may cause sleep disturbance.

Potential causes of sleep disturbance include the environment of the ICU, such as continuously bright lights and alarm sounds, the patient treatment process, pain, and ventilation. Sleep disturbance can also be caused by systemic inflammatory conditions and drugs used [105]. The mode of the ventilator also plays an important role. According to the 2018 PADIS guidelines, using the assist-control mode at night may help improve sleep quality in comparison to using the pressure-support mode [94,106].

### Table 10. Safety criteria for stopping physical rehabilitation

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea (respiration rate &gt;35 breaths/min, use of accessory muscles)</td>
<td></td>
</tr>
<tr>
<td>Cyanosis</td>
<td></td>
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<tr>
<td>Decreased oxygen saturation (oxygen saturation &lt;90%)</td>
<td></td>
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<tr>
<td>Dizziness</td>
<td></td>
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<tr>
<td>Tachycardia (increase of more than 30 beats/min in basal pulse rate)</td>
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</tr>
<tr>
<td>Patient maladjustment (sweating, tremor, etc.)</td>
<td></td>
</tr>
<tr>
<td>Patient rejection</td>
<td></td>
</tr>
<tr>
<td>Judgment by medical staff (physical therapist, nurse, etc.)</td>
<td></td>
</tr>
<tr>
<td>Fall</td>
<td></td>
</tr>
<tr>
<td>Medical device disconnection</td>
<td></td>
</tr>
</tbody>
</table>

### Table 11. Description of a sleep-promoting protocol

<table>
<thead>
<tr>
<th>Noise</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Close all doors</td>
<td></td>
</tr>
<tr>
<td>Reduction of call and machine alarm sounds (24:00–06:00)</td>
<td></td>
</tr>
<tr>
<td>Medical staff talk quietly</td>
<td></td>
</tr>
<tr>
<td>Use of earplugs</td>
<td></td>
</tr>
<tr>
<td>Light</td>
<td></td>
</tr>
<tr>
<td>Turn off central lighting in the intensive care unit (24:00–06:00)</td>
<td></td>
</tr>
<tr>
<td>Application of eyeshades</td>
<td></td>
</tr>
<tr>
<td>Use of dim bedside lighting for patient care</td>
<td></td>
</tr>
<tr>
<td>Patient care</td>
<td></td>
</tr>
<tr>
<td>Prohibition of unnecessary tests and blood collection (24:00–06:00)</td>
<td></td>
</tr>
<tr>
<td>Maintaining adequate sedation</td>
<td></td>
</tr>
<tr>
<td>Assessment of pain and use of appropriate analgesics</td>
<td></td>
</tr>
<tr>
<td>Use of the assist-control ventilation mode during the night (24:00–06:00)</td>
<td></td>
</tr>
</tbody>
</table>

**Treatment**

**KSCCM Recommendation**

- Sleep disturbance is a common risk factor for delirium in the ICU. Appropriate control of sleep disturbance can prevent delirium. (Grade B) [Update]
- A sleep-promoting protocol (offering earplugs and eyeshades, avoiding unnecessary examinations) should be used to improve the sleep of critically ill patients. (Grade A) [Update]

**Nonpharmacologic therapy**

The main factors that interfere with sleep in the ICU are often aspects of the environment, such as bright lighting, machine alarms, and ventilator alarms. Therefore, minimizing unnecessary nursing treatment or examinations at night, using earplugs and eyeshades, and similar steps can produce a significant effect on sleep disturbance at a low cost. One RCT comparing patients who used earplugs at night (n=69) with a control group that did not (n=67) reported that the use of earplugs improved the sleep quality and lowered the risk of delirium [107]. In addition, in a study that performed quality improvement activities by bundling various environmental interventions such as the use of earplugs and sleeping masks, reduction of nursing activities, and avoidance of unnecessary blood draws and examinations, the incidence of delirium was reduced (33% vs. 14%). The duration of delirium was also reduced (3.4 days vs. 1.2 days) [108]. As such, nonpharmacological treatment alone can improve sleep disorders, and appropriate nonpharmacologic strategies play a significant role in the treatment of critically ill patients (Table 11).
Various studies have been conducted on sleep-inducing drugs (melatonin, dexmedetomidine, and propofol) in treating critically ill patients. However, no drugs have shown effects. As a sedative, dexmedetomidine, which has recently been used extensively in ICUs, has been used in small studies to induce sleep only at night. It has been reported that dexmedetomidine can increase stage 2 sleep and preserve the day-night sleep cycle [109,110]. However, an RCT of 100 subjects reported that low-dose dexmedetomidine had no significant effects on sleep [84]. Considering the high cost of this drug and its hemodynamic side effects, it is not recommended for inducing sleep. Since there are few large-scale studies on drugs administered at night to promote sleep in adult ICU patients, further studies should be conducted.

**DISCUSSION**

Compared to the 2010 guidelines, we aimed to provide recent updates on the information that clinicians need to advance treatment for critically ill ICU patients. The 2021 KSCCM clinical guideline was developed based on the 2018 PADIS guideline, which was an update of the 2013 PAD guideline with the addition of rehabilitation/mobility and sleep. Routine monitoring and assessment for pain, sedation, and delirium using the most valid and reliable tools can improve outcomes associated with nonpharmacologic and pharmacologic therapeutic interventions. After initial nonpharmacologic therapy, the optimal medication choice and dose can be considered for pharmacologic treatment to treat PAD. A multi-modal analgesia strategy is needed to reduce opioid use and increase pain-modulating effects, thereby improving pain control and patient-centered outcomes. The strategy of enhancing patient comfort while maintaining a light level of sedation improves clinical outcomes. The 2021 KSCCM guideline particularly emphasizes active rehabilitation and sleep as factors influencing the recovery of critically ill ICU patients. In summary, a multidisciplinary strategy, including administering adequate pain treatment, maintaining a light level of sedation, performing routine monitoring and treatment for delirium, providing active rehabilitation in the ICU, and offering treatment for sleep disturbance, is needed to improve the clinical outcomes of critically ill ICU patients. Although these guidelines cannot offer definitive answers on all topics that are important to critical care clinicians, we believe that they can serve as a cornerstone for a comprehensive discussion on clinical issues relevant to patient management.

**CONFLICT OF INTEREST**

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

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**AUTHOR CONTRIBUTIONS**

Conceptualization: TSH. Data curation: HJL, EJH. Methodology: HJL, EJH. Writing—original draft: YS. Writing—review & editing: TSH.

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INTRODUCTION

Since the first successful lung transplantation (LTx) performed by Cooper in 1983, the number of lung transplants has increased to 69,000 over the past 30 years [1]. However, the number of donated lungs have been limited, and many patients with chronic respiratory failure requiring LTx were required to wait until they find a donor [2]. Unfortunately, some patients experience acute exacerbation of the underlying lung disease while awaiting LTx [2,3].

For a long time, although patients who underwent LTx after receiving mechanical ventilation support had poorer outcomes than non-ventilated patients, invasive mechanical ventilation has mainly served as a bridge to LTx for LTx awaiting patients who experienced acute exacerbation of lung disease [4]. Owing to the advances in technology, extracorporeal membrane oxygenation (ECMO) has been introduced as a strategy to replace or support
Lee SH  Awake ECMO as a bridge to LTx

mechanical ventilation. The rate of ECMO use as a bridge to LTx has been increasing; some study reported that the survival outcome of LTx patients who used bridged ECMO was not inferior to that of non-bridged LTx patients [4].

Furthermore, as ECMO-related techniques and experience improved, the concept of “awake ECMO” was introduced [5]. During awake ECMO, patients breathe spontaneously without the support of a mechanical ventilator and remain awake [5]. The number of attempts of employing awake ECMO as part of ECMO management and the use of awake ECMO as a bridge to LTx is increasing. In this review article, we aimed to briefly discuss the outcomes and management of ECMO and awake ECMO as a bridge to LTx.

HISTORY OF ECMO AND AWAKE ECMO

Since the successful use of ECMO in patients with respiratory failure reported in 1971 [6], the first use of ECMO as a bridge to LTx was reported in 1978 by Toronto group [7]. A 19-year-old young patient with lung damage due to exposure to smoke during a fire incident experienced problems with oxygen supply to the lungs despite using mechanical ventilation; hence, he was oxygenated using an ECMO machine before and after LTx. Although the mechanical ventilator support and oxygen therapy were completely discontinued after LTx, the patient died 18 days after LTx due to bronchial dehiscence. Subsequently, in 1985, the same Toronto group reported the use of ECMO as a bridge to LTx in a 31-year-old patient with progressive respiratory failure due to paraquat poisoning. The patient underwent right LTx after bridging ECMO, and left LTx after bridging with ECMO due to graft failure of the right transplanted lung. After re-LTx, the transplanted organ showed good lung function; however, the patient died 93 days after the first LTx due to a cerebrovascular accident caused by tracheal innominate artery fistula [8]. Although ECMO appeared to be a feasible strategy for bridging to LTx in these cases, it was considered a relative contraindication to LTx in the 1970s and the 1980s due to poor perioperative outcomes and several complications [9]. In a large-scale analysis of the prognosis according to oxygen supply using mechanical ventilation alone and ECMO with mechanical ventilation, which was initially employed in 2010, ECMO did not show a good outcome [10]. However, as the experience and techniques of ECMO accumulated and the number of centers providing ECMO support increased, the outcomes of patients who require ECMO as a bridge to LTx have not been inferior to those of non-ECMO patients [11-13].

In 2010, one center introduced the use of veno-arterial (VA) ECMO as a bridging strategy to LTx during awake and spontaneous breathing to avoid the disadvantages and complications associated with intubation and prolonged mechanical ventilation [14]. During awake ECMO, the patients are not deeply sedated and maintain spontaneous breathing without mechanical ventilation [5].

OUTCOME OF ECMO AS A BRIDGE TO LTx

Many studies on ECMO as a bridge to LTx have been conducted in the last 10 years. Chiumello et al. [15] reviewed the 1-year survival rates of LTx patients with bridged ECMO in 14 studies between 2010 and 2014. In all cases, standard veno-venous (VV) ECMO or VA ECMO was used, and the bridging time before LTx ranged from a median of 3 to 16 days. Five studies reported survival rates of 50% to 70%, four studies reported survival rates of 70% to 90%, and two studies reported survival rates of up to 90% [15]. These studies showed that the survival rates were similar between the group using ECMO bridging and that using mechanical ventilation alone [15]. However, since the number of patients included in these studies did not exceed 50 and were heterogeneous according to the centers, it was not possible to confirm whether ECMO is a better bridging strategy to LTx than mechanical ventilation. However, what is clear, the survival rate of ECMO patients increased significantly over time, from 30% in 2005 to 75% in 2010 [16].

To overcome this limitation, Hayanga et al. [4] reported the results of a survival rate analysis using the United Network for Organ Sharing database for the period 2005–2017. A total of 21,576 transplant patients were analyzed by dividing them into no bridge (n=19,783), mechanical ventilation (n=1,129), and ECMO groups (n=664). The survival rate of the ECMO bridging group significantly improved over time, and reached a similar

KEY MESSAGES

- Although the outcome of extracorporeal membrane oxygenation (ECMO) as a bridge to lung transplantation (LTx) is improving, whether it can achieve survival similar to that of non-bridged LTx patients remains controversial.
- Awake ECMO performed by a multidisciplinary team can be considered a bridge strategy for LTx as it has several advantages and is considered safe.
level as that of the survival rate in the mechanical ventilation group. Similar results have been reported in other countries [17-19], and the ECMO strategy as a bridge to LTx has been accepted.

However, in a recent meta-analysis comparing non-bridged and ECMO-bridged LTx patients using 19 studies, non-bridged LTx patients showed better 1-year to 5-year survival rates and fewer complications compared with the ECMO-bridged LTx patients [20]. In summary, whether ECMO as a bridge to LTx can achieve survival rates similar to those of non-bridged LTx patients remains controversial.

The number of patients awaiting LTx largely exceeds the number of available organs, resulting in long waiting times. A bridging strategy may be necessary if LTx is not contraindicated in patients with advanced respiratory failure. If the awaiting LTx candidates have no absolute contraindications to ECMO, a bridged ECMO strategy can be the last option during the waiting period. If the use of bridged ECMO cannot be avoided in awaiting LTx candidates, a management method is needed to lead it in a better direction.

The results of multivariate analysis in previous meta-analysis study showed that awake status (relative risk [RR], 2.7; 95% confidence interval [CI], 1.29–5.65), extubated on ECMO (RR, 5.39; 95% CI, 0.79–36), and ambulation (RR, 7.58; 95% CI, 2.16–26.62) were predictors of successful bridge to LTx [20]. Consistent with these factors, several studies have reported positive results associated with the use of ECMO as a bridge to LTx, such as awakening, minimal sedation, spontaneous breathing, and physical activity during ECMO [11,16,21]. Over the years, the use of awake ECMO to avoid tracheal intubation and mechanical ventilation has gained popularity, becoming the preferred first-line approach for patients awaiting LTx.

OUTCOME OF AWAKE ECMO AS A BRIDGE TO LTx

Fuehner et al. [22] analyzed the prognosis of patients awaiting LTx using the data of 26 awake ECMO and 34 mechanical ventilation patients; this study was the first sizable series analysis of awake ECMO as a bridge to LTx. This study found that awake ECMO had been a successful bridge to LTx, resulted in the shorter duration of mechanical ventilation use after LTx, and had a significantly higher survival rate compared with mechanical ventilation alone (80% vs. 50%) [22]. To overcome the small sample size, Schechter et al. [23] analyzed the survival rates according to the bridging type of 12,403 LTx patients from May 2005 to September 2013 using the United Network for Organ Sharing database. This study compared the survival rates of the awake ECMO, mechanical ventilation, ECMO with mechanical ventilation, and non-bridged LTx groups [23]. The 3-year survival rate after LTx in the awake ECMO group was significantly higher than that in the mechanical ventilation and ECMO with mechanical ventilation groups. When the awake group was compared with the non-bridged LTx group, the 1-year and 3-year survival rates of the awake ECMO group were 70.4% and 64.5%, while those of the non-bridged LTx group were 84.2% and 67%, respectively. Although the awake ECMO group had a worse 1-year survival rate compared with the non-bridged LTx group (70.4% vs. 84.2%, respectively), the mid-term survival of patients on ECMO alone was not significantly different (P=0.16) [23]. After adjustment using Cox analysis, the mortality risk in the awake ECMO group did not increase compared with that in the non-bridged LTx group (P=0.39). In 2019, Tipograf et al. [11] adjusted the baseline characteristics using propensity score matching between the awake ECMO and non-bridged LTx groups and reported that there was no difference in post-LTx survival rate between 70 awake ECMO patients and non-bridged LTx patients (log-rank P=0.53). Furthermore, Kim et al. recently reported that the awake ECMO group showed increased ventilator-free days, decreased intensive care unit (ICU) length of stay, and higher gait ability and lung function after LTx compared with the non-awake ECMO group [24].

These results suggest that awake ECMO is a better strategy than sedated ECMO with mechanical ventilation while awaiting LTx and support the survival outcome results, which demonstrates that the post-transplant survival of awake ECMO patients is comparable to that of non-bridged patients.

ADVANTAGES OF AWAKE ECMO

One of the advantages of awake ECMO as a bridge to LTx was maintenance of physical activity (Table 1). In 2010, Garcia et al [25], reported the possibility of physical activity in LTx patients waiting for awake ECMO. Even in healthy people, regardless of age, a 10-day bed rest induced muscle loss [26,27]. Moreover, a prospective study on critical illness myopathy showed that prolonged mechanical ventilation induced the occurrence of critical illness myopathy in more than 25% of ICU patients under mechanical ventilation [28]. Patients with critical illnesses awaiting LTx under mechanical ventilation may experience more rapid muscle loss. Active physical activity during critical
Lee SH  Awake ECMO as a bridge to LTx

Awake ECMO care is associated with improvement and maintenance of muscle strength [29]. The importance of physical activity through training for LTx candidates is already known [30].

Another advantage of awake ECMO is that spontaneous breathing induces the maintenance of respiratory muscle tone and diaphragm function [5,31]. Although spontaneous breathing may cause patient self-inflated lung injury (P-SILI) due to an increase in transpulmonary pressure owing to the exertion of vigorous effort, the effect of maintaining diaphragm function is greater than that of P-SILI in patients waiting for LTx as they have an end-stage lung disease. A previous prospective study showed that lung function could be improved by adding inspiratory muscle training to the standard pulmonary rehabilitation [32]. In another retrospective study comparing lung function 6 months after LTx according to the spontaneous breathing status of patients using ECMO as a bridge to LTx, the spontaneous breathing group showed higher lung function than the non-awake group [24].

Avoiding endotracheal intubation is also an advantage of awake ECMO. Prolonged use of endotracheal tubes can disrupt the natural defense barrier of the airway and increase the risk of pneumonia [33]. The most significant risk factor for hospital-acquired pneumonia is mechanical ventilation, and prolonged intubation increases the risk of ventilator-associated pneumonia [34]. These infections increase the risk of failure of bridges to LTx in patients with end-stage lung disease and increase the risk of mortality after LTx [35]. A study of awake ECMO as a bridge to heart transplantation showed a lower incidence of pneumonia compared to non-awake ECMO group [36].

At the time of intubation, patients may experience several complications, such as aspiration of gastric contents, vocal cord injury, laryngeal edema, pneumothorax, pneumomediatinum, hypoxemia due to esophageal intubation, and cardiac arrest [37]. Additionally, the use of an endotracheal tube increases the use of sedation and analgesics, which may cause side effects. The use of sedatives has been associated with delirium, a condition that reduces interactions with healthcare providers [5]. During awake ECMO, patients with spontaneous breathing, reduced sedative dose, and no delirium can ingest orally and have less ICU psychosis [24]. Furthermore, patients can communicate with the medical staff and participate in decision-making.

**AWAKE ECMO MANAGEMENT**

**Attempt of Using Awake ECMO**

The possibility of awake and spontaneous breathing in ECMO patients can be determined by several factors, including oxygen requirement, hypercapnia status, level of consciousness, underlying disease, and purpose of ECMO (Table 2) [38,39]. In some cases, ECMO cannulation was performed without intubation, and awake ECMO was initiated. In other studies, ECMO cannulation was inserted after intubation, mechanical ventilation was maintained, extubation was performed, and awake ECMO was initiated.

Physical activity can be attempted if the patient is hemodynamically stable, the cannulation position is stable, there is absence of bleeding at the cannulation site, the ECMO flow is stable, agitation is not observed, and anxiety is not observed, regardless of the ECMO type, including VV and VA [40,41]. A bivacal dual-lumen catheter is preferred over two independent cannulas at different venous insertion sites to allow the performance of physical activity during awake ECMO. However, physical activity can be performed even when two independent cannulas are inserted at different venous sites, including

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**Table 1. Advantages and disadvantages of awake ECMO**

<table>
<thead>
<tr>
<th>Status</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance of physical activity</td>
<td>Maintain muscle mass and strength</td>
<td>Increase the risk of catheter dislocation</td>
</tr>
<tr>
<td>Spontaneous breathing</td>
<td>Maintain respiratory muscle and diaphragm function</td>
<td>Increase transpulmonary pressure and the risk of ventilator-induced lung injury</td>
</tr>
<tr>
<td></td>
<td>Maintain the expansion of the chest wall and lungs</td>
<td>Increases oxygen consumption and CO₂ production</td>
</tr>
<tr>
<td></td>
<td>Favor venous return and maintains cardiac filling</td>
<td></td>
</tr>
<tr>
<td>Avoiding intubation</td>
<td>Reduce the risk of ventilator-associated pneumonia</td>
<td>Sometimes emergency intubation may be required.</td>
</tr>
<tr>
<td>Awake through reducing use of sedative and analgesic</td>
<td>Reduce the risk of delirium</td>
<td>Increase pain, discomfort, and anxiety</td>
</tr>
<tr>
<td></td>
<td>Enhance communication between the medical staff and the patient</td>
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<tr>
<td></td>
<td>Allow participation in decision making</td>
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ECMO: extracorporeal membrane oxygenation.
During awake ECMO, use of sedatives and analgesics, including dexmedetomidine, remifentanil, and fentanyl, may help reduce pain and anxiety. Some patients may require additional oxygen supply using a high-flow nasal cannula and non-rebreather masks.

Preparing and Monitoring during Physical Activity

Hemodynamic monitoring in awake ECMO patients did not differ from that in general ICU patients on mechanical ventilation, including continuous monitoring of all vital signs. However, the flow of ECMO should be carefully monitored in awake ECMO patients because gas exchange mainly occurs with ECMO [43]. Cannula dislocation or flow disturbance can induce life-threatening conditions due to severe hypoxemia during awake ECMO [44]. During physical activity, the medical staff should be assess the cannulation sites, observe the movement of the cannula, and monitor for reduction in blood flow due to position changes. Although several problems may occur, a previous systemic review reported that passive and active physical therapy is safe when performed by a professional ECMO multidisciplinary team [42].

Patients must be connected to a monitoring device to checking their vital signs during physical activity. Any changes in the patients’ vital signs should be noted in order to determine whether the physical activity should be continued. Patients may require increased ECMO blood flow or additional oxygen supply using a high-flow nasal cannula or mechanical ventilation during the performance of physical activities [45]. Additionally, fluid supplementation may be required to prevent chattering and to maintain the ECMO flow.

Respiratory Management during Awake ECMO

Respiratory rehabilitation before LTx can help maintain the respiratory muscle function, reduce the retention of secretions, and reduce the risk of postoperative complications [46]. Before the start of respiratory treatment, respiratory assessment including review of chest radiograph, airway status (tracheostomy status or not), movement of the chest wall and diaphragm, respiration rate, and lung sound should be performed. Furthermore, the cannula location, possible posture of patients, lung compliance, anticoagulation level, and cause of end-stage lung disease should be considered when selecting the respiratory therapy options for ECMO patients [44]. Respiratory management can be performed by positioning the patients for postural drainage, injection of saline via a closed suction port and suctioning, using manual or ventilator hyperinflation techniques, utilizing nebulizers, performing physiotherapy-assisted flexible bronchoscopy, ensuring intermittent positive pressure breathing, and using chest wall vibrator.

Physical Activity

Physical activity starts as a simple and passive activity and progresses to a more complex and active activity depending on the patient’s condition. Patients can start bed activity, including passive range of motion to resistive training and limb exercise, and gradually increase the intensity of physical activities to cycling on bed, sitting on the edge of bed, standing next to the bed, and then ambulation [40]. Various equipment including bed bikes, chair pedals, standing frames, Zimmer frames, and tilt tables can be used. If a patient can walk in place with an assistant, walking around the ICU is possible with the assistance of appropriately trained ECMO multidisciplinary team members such as nurses, physical therapists, perfusionists, respiratory therapists, and intensivist.

Nutrition

Based on current research, enteral nutrition is safe and well tolerated in adults, regardless of the ECMO type [47-49]. Early enteral nutrition is not associated with harm during VV and VA ECMO [47]. A retrospective study of 1,769 patients under VA ECMO showed that early enteral nutrition was associated with a lower mortality rate compared with late enteral nutrition [48]. Provision of appropriate nutritional support is important for improving the patients’ performance of physical activity; however, underfeeding is common in ECMO patients [49].

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Table 2. Indications and contraindications of awake ECMO

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<tr>
<th>Awake ECMO</th>
<th>Indication</th>
<th>Contraindication</th>
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<tr>
<td>Ability to protect airways</td>
<td>Hemodynamic unstable (high dose of vasoactive drugs)</td>
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<tr>
<td>Low dose or no vasoactive requirement</td>
<td>Deep sedation and muscle relaxation (RASS 3–4)</td>
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<tr>
<td>No need for high PEEP</td>
<td>Active bleeding</td>
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<td></td>
<td>Malignant arrhythmia</td>
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<td>Brain injury</td>
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<tr>
<td></td>
<td>Unstable blood flow mechanics</td>
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</tr>
<tr>
<td></td>
<td>Unexpected high respiratory rate or severe anxiety</td>
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ECMO: extracorporeal membrane oxygenation; PEEP: positive end-expiratory pressure; RASS: Richmond Agitation-Sedation Scale.
fore, the measurement or estimation of energy expenditure may be helpful in determining the proper caloric needs. However, as there are no currently available guidelines regarding the use of ECMO, it is reasonable to follow the current guidelines for critically ill patients until further research is available [47].

Problem during Awake ECMO
According to the level of consciousness and physical activities performed during ECMO, the patients may experience more problems, which were not considered in conventional ECMO (Table 3) [50]. The patients may experience increased CO₂ production and require higher oxygen level as the work of breathing is increased. To overcome these problems, the medical staff should adjust the ECMO blood flow and sweep gas, and the patients can receive additional oxygen support using a high-flow nasal cannula. The patients may need to undergo tracheostomy to decrease the work of breathing and receive proper respiratory tract management.

Anxiety and agitation may induce vigorous effort, leading to a P-SILI and increase the work of breathing. Some drugs, including dexmedetomidine and remifentanil, may be helpful. Excessive cardiac output can lead to hypoxemia compared with ECMO flow-induced hypoxemia, and the administration of beta-blockers may help in relieving hypoxemia [51].

Sometimes, while maintaining spontaneous respiration and physical activity, ECMO flow reduction or chattering may be induced by inferior vena cava collapse [50,52]. Hypovolemia can be corrected with fluid therapy, and light sedation can help if the respiratory effort is excessive. Additionally, if the drain catheter is located in the femoral vein, the catheter tip can be moved down the diaphragm due to the movement of the leg. In this case, the location of the drain catheter may be adjusted or the ECMO flow may be lowered if oxygen saturation is maintained. Occasionally, chattering may occur because of bending, and the circuit line should be checked.

Sometimes, the patients may develop right-sided heart failure and eventually die during VV ECMO. Monitoring using echocardiography during ECMO helps detect biventricular size and function [52]. In right-sided heart failure case, another cannula should be added to the system for veno-arteriovenous ECMO or the oxy-right ventricular assist device to deliver blood to the arterial circulation in order to provide direct circulatory support [53].

Problems with ECMO machine operation, including catheter dislocation, de-cannulation, circuit rupture, and pump failure, can occur unexpectedly. In case of catheter dislocation, cannulation, or circuit rupture, the catheter should be clamped immediately, the pump should be turned off, help should be sought, and compress and intubation should be performed [50]. Circuit changes must be made while stabilizing the patients’ vital signs. When the pump fails, it should be operated manually using a hand crake, and the cause must be corrected [50].

| Table 3. Problems during awake ECMO |
|-------------------------------|------------------------------------|--------------------------------|
| Problem                           | Status of occurrence            | Challenge to be solved                  |
| Hypoxemia                        | Increases oxygen consumption due to the increased work of breathing | Adjustment of the ECMO flow               |
|                                 | Difficulty removing secretions    | Additional oxygen supply using HFNC and mask Tracheostomy |
| Anxiety and agitation            | Discomfort due to the presence of devices and lines | Use of low-dose analgesics and sedative drugs including dexmedetomidine and remifentanil |
|                                 | Increases the respiratory rate    | Use of low-dose beta-blockers           |
| Chattering of catheter           | Bending of circuit               | Correction circuit                       |
|                                 | Hypervolemia                      | Fluid supply                            |
|                                 | Catheter tip migration due to activity | ECMO flow adjustment                      |
|                                 |                                    | Catheter position adjustment            |
| Progress right heart dysfunction or pulmonary hypertension | In VV ECMO | Change to VAV ECMO or the oxy-right ventricular assist device |
| Machine problem                 | Catheter decannulation/circuit rupture | Clamping the catheter, turning off the pump, calling for help, compression, and intubation → Circuit change |
|                                 | Pump failure                      | Operated manually using hand crake → Correcting the underlying cause or changing the machine |

ECMO: extracorporeal membrane oxygenation; HFNC: high-flow nasal cannula; VV: veno-venous; VAV: veno-arteriovenous
LIMITATION

Aforementioned many studies showed successful awake ECMO as a bridge to LTx, however, there are still insufficient studies on failure rate of awake ECMO, rate of emergency intubation during awake ECMO, and unexpected complications and events during awake ECMO. Therefore, there may be bias, we should read careful about these paper.

CONCLUSION

With advances in ECMO technology, patients who were previously excluded from the transplant waiting list due to disease exacerbation can now be bridged with ECMO; as a result, the rate of ECMO use in patients awaiting LTx has increased. Although it remains controversial whether ECMO as a bridge to LTx can achieve similar outcomes as that in unbridged LTx patients, awake ECMO showed several benefits and favorable outcomes. In cases requiring ECMO or mechanical ventilation due to unavoidable exacerbation in awaiting LTx patients, awake ECMO strategy performed by an appropriately trained ECMO multi-disciplinary team can be useful compared with mechanical ventilation or conventional ECMO strategy.

CONFLICT OF INTEREST

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

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Brain–lung interaction: a vicious cycle in traumatic brain injury

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The brain–lung interaction can seriously affect patients with traumatic brain injury, triggering a vicious cycle that worsens patient prognosis. Although the mechanisms of the interaction are not fully elucidated, several hypotheses, notably the "blast injury" theory or "double hit" model, have been proposed and constitute the basis of its development and progression. The brain and lungs strongly interact via complex pathways from the brain to the lungs but also from the lungs to the brain. The main pulmonary disorders that occur after brain injuries are neurogenic pulmonary edema, acute respiratory distress syndrome, and ventilator-associated pneumonia, and the principal brain disorders after lung injuries include brain hypoxia and intracranial hypertension. All of these conditions are key considerations for management therapies after traumatic brain injury and need exceptional case-by-case monitoring to avoid neurological or pulmonary complications. This review aims to describe the history, pathophysiology, risk factors, characteristics, and complications of brain–lung and lung–brain interactions and the impact of different old and recent modalities of treatment in the context of traumatic brain injury.

Key Words: lung injury; neurocritical care; neurogenic pulmonary edema; traumatic brain injuries; ventilator–induced lung injury

INTRODUCTION

Traumatic brain injury (TBI) is one of the leading causes of death and disability worldwide, with enormous economic and social consequences [1]. TBI results from direct damage to the brain caused by an external, physical force, which can lead to a state of decreased consciousness, physical functioning, or deterioration of cognitive ability [2]. Many secondary lesions in patients with TBI occur in a medium-long term period, and the appearance of brain and pulmonary complications is highly prevalent. Direct brain injury and altered levels of consciousness decrease the protection of the airways and alter the natural defense barrier, which adds to reduced mobility and multiple pathophysiological deficits inherent to the injury [3].
and triggers several lung injuries, like neurogenic pulmonary edema (NPE), acute respiratory distress syndrome (ARDS), and ventilation-associated pneumonia (VAP). In the same way, lung injuries can affect the brain due to alterations in pulmonary physiology having repercussions at the systemic level, leading to neurological disorders which can be triggered mainly by hypoxia and intracranial hypertension [3,4].

The brain and lungs share fundamental connections that are compromised in patients with TBI. This injury becomes a vicious cycle that worsens patient condition (Figure 1). Considering the increasing global incidence of TBI, deficient access to healthcare in many parts of the world, and inadequate methods of treatment [1], we present a narrative review of the available evidence on the mechanisms of brain-lung interaction in patients with trauma as well as new therapeutic implications and possible management strategies that could reduce brain and pulmonary complications and improve the prognosis of patients in order to provide a basis for future research.

HISTORY

Extracranial complications frequently occur in patients with TBI; among them, pulmonary disorders are common and deteriorate patient condition, leading to serious neurological outcomes. Brown-Séquard [5] was the first to describe the interaction between TBI and the lungs in 1871 in his experimental traumatic injury to the pons of guinea pigs that resulted in pulmonary hemorrhage and edema. In 1969, Simmons et al. [6] evaluated an autopsy series of patients who died from TBI that reported the vast majority of those who died within few minutes after trauma to have pulmonary edema, which allowed them to affirm that TBI is decisive in the development of pulmonary edema with consequent respiratory dysfunction. In 1976, Theodore and Robin introduced the “explosion theory” to explain NPE in patients with TBI [7] that declared an excess of catecholamines and consequent positive regulation of sympathetic signal transduction to be responsible for the increase in pulmonary venous pressure and transudative edema. Finally, although NPE was estimated to have an incidence of only 1% after cerebral trauma in 1997, a mortality of 60%–100% was demonstrated regardless of its etiology, which triggered the alarms to consider it a life-threatening condition after it was demonstrated to increase of intracranial pressure (ICP), where pulmonary hemorrhage and edema. In 1969, Simmons et al. [6] evaluated an autopsy series of patients who died from TBI that reported the vast majority of those who died within few minutes after trauma to have pulmonary edema, which allowed them to affirm that TBI is decisive in the development of pulmonary edema with consequent respiratory dysfunction. In 1976, Theodore and Robin introduced the “explosion theory” to explain NPE in patients with TBI [7] that declared an excess of catecholamines and consequent positive regulation of sympathetic signal transduction to be responsible for the increase in pulmonary venous pressure and transudative edema. Finally, although NPE was estimated to have an incidence of only 1% after cerebral trauma in 1997, a mortality of 60%–100% was demonstrated regardless of its etiology, which triggered the alarms to consider it a life-threatening condition after it was demonstrated to increase of intracranial pressure (ICP), where

Figure 1. Vicious circle of the interaction between acute lung injury in patients with traumatic brain injury: a double impact model.

Acute and Critical Care 2022 February 37(1):35-44

https://www.accjournal.org

immediate therapeutic interventions are essential [8].

Likewise, in terms of frequent pulmonary complications, ARDS is also notable. Its concept has evolved from the old name idiopathic pulmonary anasarca, postulated by Laënnec in 1821, until its recent definition in Berlin [9]. In 1967, Ashbaugh et al. [10] presented the concept of ARDS as respiratory distress syndrome, which was improved in 1988 by Murray et al. [11] by including the description of a multi-section system. Later, the European-American Consensus Conference conceptualized the criteria for acute lung injury (ALI). However, it was decided not to use the ALI term and to stratify ARDS into three levels of severity in the more recent Berlin definition [9].

In 1997, Bratton and Davis [12] evaluated the incidence of ALI in comatose patients after isolated TBI and found that it was 20%, showing a three-fold greater probability of dying or surviving in a vegetative state. In a study published in 2003, it was reported that 31% of patients with severe TBI developed ALI, with a greater number of days in mechanical ventilation (MV), a worse neurological outcome, and mortality of 38% [13]. The presence of ALI or ARDS complicates the treatment of patients with TBI because hypoxia causes additional damage to the brain and because therapies used to protect the lungs and improve patient oxygenation can reduce cerebral blood flow and increase ICP [14]. In a 20-year retrospective cohort study of patients with TBI, an increase in the prevalence of ALI or ARDS was found, and a greater association with comorbidities, such as congestive heart failure, hypertension, chronic obstructive pulmonary disease, chronic kidney disease, and liver failure, as well as increased risk of sepsis, multi-organ dysfunction, and in-hospital mortality was found [15].

There is a high frequency of infection in patients with TBI due to a predisposition attributed to compromised host defenses after brain trauma and the need for MV in these patients [16]. In 1992, Piek et al. [17] evaluated the determinants of recovery after severe brain trauma and found that pneumonia was the second most frequent complication (40.6%) on the fifth to tenth days after the trauma; furthermore, they emphasized the fact that many of them were not preventable in critically ill patients and could only be managed through quick diagnosis, prompt etiology identification, and opportune treatment [17]. Later, pneumonia was found in 60% of 125 patients with closed head trauma. Of which, 47.8% corresponded to early pneumonia and were associated with lower scores on the Glasgow coma scale (GCS), longer intubation time, intensive care duration, and hospitalization [18].

VAP is among the most important subtypes of nosocomial infections, and the incidence of this type of pneumonia in patients with brain injury ranges from 28% to 40% [19]. In 1999, Ranieri et al. [20] demonstrated for the first time that MV induced a cytokine response in the lungs and plasma, which was associated with higher rates of multi-organ failure. However, they suggested that attenuation of this inflammatory response could be a useful strategy to minimize overstretching and cell recruitment in lungs, with possible improvements in clinical outcomes. In 2004, Bronchard et al. [21] published a prospective observational study of patients with TBI who required tracheal intubation for neurological reasons and ventilation for at least 2 days and reported a 41.3% incidence of early-onset pneumonia with low arterial oxygen pressure (PaO₂), decreased inspired fraction of oxygen (FiO₂), fever, hypotension, and intracranial hypertension. They concluded that early-onset pneumonia led to secondary lesions and neurological deterioration.

BRAIN–LUNG INTERACTIONS IN BRAIN TRAUMA

From Brain to Lung Physiopathology

Shortly after presenting brain damage of any kind, preclinical lung injury appears even without obvious symptoms—this effect manifests with alterations in the mechanics of the respiratory system and hypoxemia [22]. Although the mechanisms by which brain damage leads to alterations in lung function are not clear, the development of NPE, inflammatory processes, neurotransmitter-related compromise, and even adverse effects secondary to the administration of neuroprotective therapies can be considered fundamental [23]. A well-recognized theory to explain the pathophysiology responsible for lung damage is “blunt injury,” which suggests that a sympathetic storm after a sudden increase in ICP induces a massive release of catecholamines. This results in a transient increase in intravascular pressure, rupture of the alveolar-capillary membrane, and consequent development of NPE [22].

As well as NPE constituting a fundamental part of the genesis of pulmonary dysfunction after TBI, the systemic inflammatory response also plays an important role in its development [24]. The intracranial inflammatory response occurs after brain injury, and pro-inflammatory cytokines, such as interleukins (IL-1, IL-6, IL-8) and tumor necrosis factor, are produced locally in the injured brain tissue. First, microglia and astrocytes are the main sources of inflammatory mediators. Then, the
alteration of blood-brain barrier permeability allows its discharge into systemic circulation. Likewise, all this production of inflammatory mediators (“first hit”) concomitant to the procedures used in the treatment of patients with TBI; such as MV; surgical procedures; or complications, namely infections (“second hit”), make up the recently described “double hit” model (Figure 1) [4].

Neurogenic pulmonary edema
NPE is a clinical condition that manifests as acute respiratory distress, occurring secondary to insult to the central nervous system (CNS). By definition, this condition is characterized by a large accumulation of extravascular pulmonary fluid, which appears suddenly and immediately after serious lesions of the CNS, mostly the brainstem [25]. If the clinical presentation is evident, the diagnosis should be assumed when acute pulmonary edema is observed in association with CNS injury in the absence of primary pulmonary or cardiovascular injury. However, this idea is imprecise because the literature does not present a complete understanding of the exact pathogenesis [26-28].

Nowadays, it is known that alteration of the CNS causes a sympathetic overflow, leading to a state of systemic vasoconstriction. This leads to the accumulation of blood from systemic circulation into the pulmonary circulation, resulting in pulmonary hypertension and an increase in pulmonary capillary hydrostatic pressure [29]. The change in pressures is responsible for the leakage of intravascular fluid to both the alveoli and the pulmonary interstitial space through two mechanisms: first, Starling forces, and second, changes in permeability in the capillary walls [25].

Elevated systemic arterial pressure and increased left atrial and pulmonary hydrostatic pressure, culminating in pulmonary edema, are attributed to peaks in sympathetic activity, particularly α-adrenergic, induced by lesions of the hypothalamus or spinal cord [30]. This sympathetic hyperactivity is triggered by a sudden increase in ICP or a decrease in cerebral blood flow [31].

Acute respiratory distress
In patients with brain lesions, a high incidence rate of ARDS has been described [4]. This affects the morbidity and mortality of patients with brain lesions in all cases, increasing inpatient mortality until three times when it appears after TBI. Risk factors for the development of ARDS have been identified. First, the severity of the initial brain injury characterized by a low GCS and abnormalities in initial brain computed tomography (CT) (displacement midline and global CT findings) and second, induced hypertension, administration of vasoactive drugs, and a history of drug abuse have been reported to be independent factors of ARDS in severe TBI. Similarly, there are general risk factors, such as male sex; young age; ethnicity; and a history of chronic arterial hypertension, diabetes, chronic obstructive pulmonary disease, development of sepsis, cardiovascular, renal, and hematological dysfunctions [15,32]. On the other hand, it has been determined over the years that the distribution of ARDS has a bimodal character, consisting of an early peak on the second or third day after the start of MV and a later peak on the eighth or ninth day after the start of ventilation, often related to pneumonia [4].

Ventilation-associated pneumonia
VAP is defined as an infection of the lung parenchyma that occurs in patients exposed to invasive MV for at least 48 hours. Currently, this pathology remains one of the most frequent infections in those patients who require invasive MV, and despite recent advances in microbiological tools and epidemiology, the diagnostic criteria remain controversial [33]. MV is an effective life-saving intervention method for critically ill patients. Thus, it is widely used in intensive care units (ICUs). This strategy allows the supply of oxygen and the elimination of carbon dioxide (CO₂) with strict control of PaO₂ and PaCO₂. The main objective of MV is the prevention of secondary cerebral ischemia and incrementally positive neurological outcomes. However, prolonged MV can increase the risk of infection and a variety of complications [4].

Ventilation time and ICU stay have been reported to be significantly longer in patients with VAP than in those without VAP. An Egyptian study found that the incidence of VAP increased from 5% in patients who received 1 day of MV to 65% in patients who received 30 days of MV [34]. An artificial airway must be established to perform MV, which changes the defense function of the resident airway mucosa and decreases the ability to swallow and the ability of cilia to clear. Subsequently, bacteria can enter the lower respiratory tract directly or cross the space between the wall of the tracheal tube and the airways to begin the infectious process [35].

VAP has been frequently identified in neurological patients due to decreased level of consciousness, micro aspirations, and even massive aspiration. The main risk factors for developing VAP in patients with brain injury are polytransfusion, age, obesity, diabetes, immunosuppression status, chronic
within the previous 90 days. A study conducted in Serbia in 2015 showed that the incidence of VAP in patients with severe TBI was up to 49.7%, much higher than the mean incidence of VAP without TBI [36].

The microorganisms that cause VAP vary with respect to the duration of MV; the length of stay in the ICU; the previous, prolonged or irresponsible use of antimicrobials; the local microbial prevalence; and the appearance of any potential epidemic phenomenon in a given ICU. The most common gram-negative bacteria involved in VAP are Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, and Acinetobacter species, while Staphylococcus aureus is the main gram-positive microorganism, being the most common pathogen reported in VAP in patients with severe TBI [37,38].

In general, it is recognized that a normal oropharyngeal flora is generally involved in VAP that occurs in the first 4 days of hospitalization in previously healthy patients who have not received or receive antibiotics regularly or inadequately. On the other hand, in patients who present the clinical characteristics of VAP after at least 5 days of hospitalization and who present its risk factors, it is more likely that their infection is due to multidrug-resistant (MDR) pathogens. However, MDR pathogens can be isolated in early-onset VAP, primarily in the presence of certain risk factors, such as antimicrobial exposure within the previous 90 days [39,40].

**From the Lung to the Brain Physiopathology**

Due to a large number of communication pathways between the peripheral nervous system and the CNS [9], lung injuries or pathologies that affect proper oxygenation can lead to alterations at the neuronal level, like memory problems, disorientation, cognition, and language alterations, through various routes [41]. Among these pathways, we find three to be fundamental: humoral, neural, and cellular. The first pathway consists of the recruitment of monocytes or macrophages in the lungs, which increases the levels of inflammatory mediators that can directly reach the CNS through the humoral route. The neuronal pathway refers to the fact that there is a connection between the brain and the nucleus of the solitary tract through the afferents of the vagal pathway. Finally, the cellular pathway is directly regulated by the release of tumor necrosis factor in the lungs that stimulates the release of monocyte chemoattractant protein-1 at the brain level, which increases the recruitment of activated monocytes both at the level of the CNS and the periphery nervous system [9].

**Cerebral hypoxia**

Hypoxemia is a potential risk factor for the development of long-term cognitive impairment. Lower PaO₂ values were associated with cognitive impairment in general and executive dysfunction specifically. Long-term neuropsychological damage is common in survivors of ALI [42]. Despite the mechanism of connection or integration that causes neurological alterations not being widely understood, several experimental studies have tried to explain the mechanism by which lung damage can lead to neurological disorders and uncover the role of hypoxemia in these changes. In a 2005 experimental study with 14 pigs, Fries et al. [43] induced hypoxemia in two groups by repeated lung lavages (lung injury group) or by reducing the inspired oxygen fraction (hypoxia-only group), concluding that the same degree of hypoxemia induced in the lavage model of ALI results in greater brain damage, assessed by S-100 protein and histopathologic findings when compared to the group in which hypoxemia was induced at the same degree by reducing the inspired oxygen fraction. This suggests that ALI leads to neuropathological changes independent of hypoxemia [43].

Bickenbach et al. [44] also examined the influence of ALI and hypoxia on neurological outcomes in pigs. In their study, they demonstrated that neurocognitive compromise after ALI seems due to a more pronounced inflammatory response and complex MV. However, these changes only resulted in mild changes in histopathology in terms of perivascular inflammation in the hippocampal CA1 sector, and the caudate nucleus and the putamen were not significantly different between the groups [44].

Mechanisms for the deterioration of neurologic function after lung injury remain unclear and may include hypoxia and the effects of MV and its consequential inflammatory response [44]. A systematic review in 2021 showed an association between MV and acute cognitive impairment, and preclinical papers showed acute cognitive impairment after MV, describing greater neuroinflammation and lower cognitive scores in subjects with a longer MV duration [45]. On the other hand, patients with ARDS may experience long periods of hypoxia, leading to the hypothesis that they might develop brain lesions and atrophy similar to those observed in other disorders with concomitant hypoxia [46]. Kamuf et al. [47] carried out the first
study focusing on the neuroinflammatory injury potential of early ARDS, and they found hints indicating an increased cerebral expression of inflammatory cytokines within 6 hours after the onset of lung injury but no signs of histopathologic injury [47]. The mechanism of changes in the brain-lung relationship that occur in hypoxic situations could be explained by specific signaling pathways. Some of these pathways have been established in animal models, such as in naked mole-rat hypoxia models, in which hypoxia altered the Akt/mammalian target of rapamycin pathway, which correlated with a general decrease in the ribosomal protein biosynthesis machinery activity in the lungs and brain [48].

Intracranial hypertension
In brain-injured patients, especially those in critical care, there is a serious detriment to respiratory function with the elevation of PaCO₂. This directly causes the vasodilation of cerebral arteries and a consequent increase in cerebral blood volume, which might result in a higher ICP if intracranial compliance is reduced [22]. Moreover, PaO₂ and PaCO₂ can also change with MV and positive end-expiratory pressure (PEEP), which raise ICP by increasing pleural pressure and diminishing venous return. [49]. Intracranial hypertension and ARDS were thought to be independent pathological entities, but recent results have shown that they both interact and actually trigger each other. A study in mechanically ventilated pigs found that ARDS induces a systemic inflammatory response with aberrantly elevated cytokines and neutrophil counts, which has a detrimental effect on the brain and acts synergistically with intracranial hypertension [50].

Therapeutic Implications: the Conflict between the Brain and Lungs
The management of patients with TBI represents a great challenge and includes multiple strategies that seek to preserve the brain-lung balance. The objective of ventilatory support is to maintain adequate oxygenation (PaO₂ ≥60 mm Hg) and avoid hypercapnia [51] in addition to protecting ICP and thus preventing secondary brain injury [22,52]. For this reason, the traditional ventilatory strategy for the prevention and treatment of intracranial hypertension was to impart high tidal volume to maintain mild hypocapnia (PaCO₂ 30 to 35 mm Hg) [51]. However, it has been shown that high tidal volume can affect the brain, inducing intracranial hypertension and causing a deleterious event (second hit) in the lung, which is a particularly sensitive organ [22].

A neurological study of ICU patients established that high tidal volume ventilation was an independent predictor of ARDS in patients with severe brain injury [53]. Likewise, a study in rats found that low tidal volume minimized lung morphological and functional changes, improving oxygenation and reducing lung damage compared to the use of high tidal volumes [54]. Thus, research suggests that maintaining a low tidal volume could be more beneficial in patients with or without ARDS since it reduces the risk of pulmonary complications after TBI [55].

According to the guidelines of the “Brain Trauma Foundation,” prolonged prophylactic hyperventilation with PaCO₂ ≤25 mm Hg is not recommended for the reduction of elevated ICP, and it should be avoided, especially during the first 24 hours after the injury when the cerebral blood flow often declines critically. In addition, it is mentioned that hyperventilation with measurements of jugular oxygen saturation or partial pressure of oxygen of brain tissue to monitor oxygen supply is only temporarily recommended [56]. These recommendations are based on the fact that hyperventilation can be harmful since severe hypocapnia and subsequent cerebral vasoconstriction can lead to hypoxia in brain tissue and compromised blood flow velocities and compliance. Finally, when ARDS and TBI coexist, it is necessary to find a balance between CO₂ control and lung protection, although there are no absolute contraindications for the use of protective ventilation in the treatment of TBI without significant intracranial hypertension. Thus, PaCO₂ values should be established on a case-by-case basis in accordance with ICP [51,52].

On the other hand, PEEP increases pleural and intrathoracic pressure and, consequently, can alter central venous return and cause an increase in ICP; therefore, the management of null or low PEEP (≤5 cm H₂O) has been recommended in mechanically ventilated brain-injured patients [57]. However, the transmission of PEEP into the thoracic cavity depends on the properties of the lungs and chest wall. An experimental study conducted by Chapin et al. [58] showed that when the lung elastance is high, PEEP can minimize airway pressure transmission, whereas high elastance in the chest wall can significantly increase pleural pressure and eventually ICP. Both ideas were supported by several studies. First, a prospective study of 21 comatose patients with severe head injury or subarachnoid hemorrhage who required MV and PEEP demonstrated that PEEP exerts no significant effects on cerebral hemodynamics in patients with high respiratory system elastance [49]. Likewise, in a prospective pilot study that evaluated 20 patients...
with TBI and ARDS, it was reported that an increase in PEEP up to 15 cm H₂O resulted in an increase in oxygen pressure and saturation in brain tissue without an increase in ICP or a decrease in cerebral perfusion pressure (CPP) [59]. Similarly, a study found that the effect of PEEP on ICP was more profound in patients with higher elastance chest walls [60]. Nevertheless, PEEP can alter CPP in hypovolemic conditions [57], which seems to indicate that an increase in PEEP can be safely applied to impart beneficial brain effects in brain-injured ARDS patients as long as they are normovolemic with high lung elastance and low chest wall elastance.

Recruitment maneuvers (RMs) have been reported as useful strategies capable of improving oxygenation, restoring alveolar recruitment, and optimizing ventilation-perfusion mismatch [52]. However, for the same reasons as PEEP, RMs could lower blood pressure and increase ICP by interfering with the return of venous blood, causing an elevation in intrathoracic pressure. Thus, the use of RMs can be safe only with strict monitoring of systemic and cerebral parameters and the use of progressive maneuvers [4].

Likewise, the prone position has been shown to increase oxygenation through different mechanisms, such as net recruitment, increased homogeneous distribution of alveolar ventilation, and protection from ventilation-associated lung injury [4]. The clinical case of a patient with thoracic and brain trauma who subsequently developed ARDS showed an improvement in lung function indices with moderate and very transient effects of ICP that resolved shortly after the change in position (supine position) [61]. Nevertheless, this maneuver has been poorly studied in patients with brain injuries, so prone positioning may be considered in patients with concurrent severe ARDS (PaO₂/FiO₂ ratio <150) and TBI but do not have significant ICP elevation [62].

It has recently been shown that inflammasomes NLRP1,2,3 (NOD-like receptors purine domain-containing) NLRC4 (NOD-like receptor CARD domain-containing), and AIM2 (absent in melanoma 2) play a role in TBI, facilitating the rapid activation of the innate immune response [63], which leads to exaggerated systemic inflammation and contributes to the damage of other organs, favoring the pathogenesis of ALI/ARDS after TBI [64]. Therefore, these inflammasome proteins can serve as possible biomarkers to assess the severity of injury and as possible therapeutic targets for inhibition [63].

Currently, there are no effective therapies to mitigate disability. However, new studies are paving the way for future interventions. In a study by Lee et al. [65], they found evidence that inhibiting neuronal death and preventing the activation of the inflammasome provides beneficial effects by reducing the potentially harmful consequences of activated microglia and leukocyte infiltration after penetrating TBI. Also, inflammasome inhibition through the use of neutralizing antibodies against inflammasome proteins has been tested and has had some success in preclinical models of TBI [63].

In a study evaluating the effects of enoxaparin after TBI, a significant decrease in the ALI score as well as neutrophil and macrophage infiltration into the lungs 24 hours after injury was found. This study demonstrated that enoxaparin attenuates ALI and inhibits the expression of the inflammasome in the brain and lungs after TBI, supporting the hypothesis that the inhibition of the neural-respiratory inflammasome axis that is activated after TBI may have therapeutic potential [66].

Regarding NPE patients, few studies have reported on specific treatments in humans, and only a few studies in animals have focused on treatment with α-blockers to limit massive sympathetic discharge after brain injuries [4]. This emphasizes the need for more studies with directed strategies to reduce the organic consequences and improve patient prognosis.

**CONCLUSION**

The brain-lung relationship arises from the interaction of several factors which are triggered by trauma responses and can communicate between the organs through different pathways. Nevertheless, almost always after a TBI, only the brain effect at the pulmonary level is considered, with very little consideration of the detrimental reverse consequences. Acute lung damage caused by ARDS or MV can worsen neurological functions in patients with TBI by humoral, neuronal, and cellular communications and by the interaction of numerous elements released locally or systemically in trauma response. Hence, therapeutic strategies should be able to minimize the impact of TBI in critical patients, both at the pulmonary and neurological levels.

MV can have a beneficial effect on oxygenation and cerebral perfusion in patients with TBI. However, the estimation of tidal volume, PEEP, and RMs is also necessary in addition to considering systemic and cerebral parameters, such as ICP, PaCO₂, PaO₂, and properties of the lungs and chest wall due to the close relationship that they have to the elevation of ICP. Finally, we conclude that the management of patients with TBI should be established on a case-by-case basis considering individual characteristics to avoid the appearance of neurological and...

pulmonary complications that influence prognosis or constitute long-term sequelae with greater morbidity and mortality, additional costs to health services, and the inevitable decrease in patient quality of life. Although new strategies targeting the inflammatory cascade are being investigated, experimental and clinical studies are needed to evaluate the brain and lung level effects.

CONFLICT OF INTEREST

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

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A machine learning model for predicting favorable outcome in severe traumatic brain injury patients after 6 months

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INTRODUCTION

Traumatic brain injury (TBI) is one of the most common and costly health and socioeconomic problems worldwide. The incidence of TBI is higher than that of complex diseases such as breast cancer, AIDS, multiple sclerosis, and Parkinson disease, such that TBI is considered the leading cause of mortality and disability amongst individuals under 45 years of age. This brain injury is the cause of approximately 50,000 deaths per year in the United States [1–3].
It is reported that around 10%–15% of patients with TBI need specialist care leading to high costs for both individuals and society. Accurate assessment and classification of patients with TBI could assist with diagnosing, optimizing treatment procedures, improving clinical outcomes, and may result in substantial economic savings.

A common measure for long-term functional outcomes in TBI patients is the Glasgow outcome scale (GOS) or its extended version extended Glasgow outcome scale (GOSE), which consists of eight ordered categories [4]. These measures are acknowledged to be standard means of describing outcomes in head injury patients due to several advantages such as their reliability, validity, stability, simplicity, availability, and ease of access. Considering the costs of TBI, developing a model capable of predicting favorable or unfavorable GOS/GOSE outcomes in advance might assist the clinicians to optimize the management and treatment of this injury.

Several prediction models using machine learning tools were developed to predict GOS based on medical image modalities [5–8]. Focusing on a specific age group, Hale et al. [5,6] used imaging techniques that display many strengths, such as consistency of computed tomography or ubiquitous usage of magnetic resonance imaging, as well as the multimodal techniques based on this imaging techniques. Nonetheless, imaging data quality might be uneven, have variabilities in data types, atlases, interpretations, and user specifics [9]. Folweiler et al. [10] utilized clustering, which deals with the challenge of picking a confident evaluation method. On the other hand, a combination of machine learning methods and information datasets of patients, including the GOS parameter, was used for predicting the prediction models in some of the previous works [11–15]. Employing crucial parameters for outcome prediction is absent in [12,14], while the sample size in [13] is not sufficiently high and hence might not be reliable enough. Moreover, in Eftekhar et al.’s study [15], a specific portion of data was considered, and the time of mortality evaluation was not mentioned clearly. Conveniently, reporting 100% sensitivity for mortality prediction creates an unrealistic picture of the model performance and is a sign of a severe overfitting problem in [11]. In two studies [16,17], authors only focused on feature selection methods, and important features and classification models were not explored in these works. One major problem in [16] is the value of 58.9% for sensitivity that is lower than existing standards; another is the 89.2% specificity that shows unbalanced accuracy for different groups. A reliable model to predict the outcome of TBI could be used as a decision aid system for prognosis, treatment, and neurosurgery with better quality.

In this research, we explored the possibility of developing a machine learning-based model for predicting “favorable” or “unfavorable” outcome after 6 months in severe TBI patients. The parameters measured at admission were used as features (predictors), and three different machine learning models were examined.

**MATERIALS AND METHODS**

The procedures used in this study were performed in accordance with the ethical standards of the Ethics Committee of Human Experimentation of Shiraz University of Medical Sciences and in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from the participants included in the study. The study protocol has been approved by the Ethics Committee of Human Experimentation of Shiraz University of Medical Sciences (SUMS), Shiraz, Iran (Ethic #IR.SUMS.REC.1397.296).

The objective of this work was to develop a model capable of predicting GOSE for TBI patients after 6 months. Precisely, the model was to predict and decide whether GOSE will be “favorable” or “unfavorable” outcome after 6 months in severe TBI patients. We considered GOSE > 4 as “favorable” and GOSE ≤4 as “unfavorable.” The process consisted of three steps: data collection, model development, and evaluation.

**Data Collection**

Nine features/variables from 2,381 patients admitted to the neuro-intensive care unit of Rajaee (Emtiaz) Hospital (Shiraz, Iran) between 2015 and 2017 were collected and used as pre-
dictors. These features were parameters measured upon admission including age, sex, Rotterdam index, blood sugar (BS) level, prothrombin time internacional normalized ratio (PT-INR), GCS motor response, and systolic blood pressure (SBP). The extended Glasgow outcome scale (GOSE) was measured by experts six months after severe TBI trauma.

The GOSE was subsequently categorized into “unfavorable” (GOSE <5 meaning dead, vegetative state, or severe disability) or “favorable” (GOSE > 4 meaning mild disability or full recovery) outcomes. Ultimately, 470 cases (27.9%) were considered as “unfavorable” and 1,212 cases (72.1%) were categorized as “favorable.”

Model Development
The model development process consisted of two steps: feature selection and classification. Feature selection was used to identify and remove inappropriate variables from the feature set. The remaining subset of variables was included in the model as the predictors. For this purpose, we employed the sequential forward selection (SFS) technique in which features were serially added to the model one at a time until there were no remaining candidate features that significantly improved the model performance. We used the classification accuracy as the objective function (the wrapper method). The SFS algorithms are discussed in [18]. To construct the predicting model, three well-known algorithms were explored: logistic regression (LR), random forest (RF), and support vector machines.

Logistic regression
LR is a classification algorithm (statistical model) which estimates the probability that a given sample belongs to a certain class. The estimation is conducted using a sigmoid (logistic) function applied to the weighted average of the predictors. The learning procedure is finding the value of these weights [19]. For binary classification, the class label is determined using the thresholding techniques with a threshold value of 0.5 in general. However, the threshold value can be adjusted to balance the sensitivity or specificity when needed.

Random forest
RF is a kind of ensemble classifier based on a different combination of decision trees. Apart from the standard trees, where each node is split based on the most promising splits among all the variables, RF splits each node using the best variable. The best feature is chosen from a subset of randomly assembled variables. This concept has made RF robust against overfitting. The process of developing a RF classifier is well discussed in [20,21].

Support vector machines
Support vector machines emphasize seeking a decision boundary that minimizes the generalization error. This is achieved by maximizing margin. For the problems with non-linearly separable classes, the data is mapped onto a new space using kernels such that in the new space the data is linearly separable and the SVM optimization problem will fruitfully yield a separating hyperplane [19,22].

Evaluation
The performance of the proposed predicting model was assessed using three performance indices including sensitivity, specificity, and accuracy. Additionally, the area under the curve (AUC) of the receiver operating characteristic (ROC) was used to evaluate the capability of the predictors in discriminating the 6-month post-trauma survival status of the patients. In estimating these indices, we used the k-fold cross-validation procedure to ensure unbiased estimation and ultimately unbiased evaluation of the developed prediction models. The given dataset was randomly divided into k subsets, and then the classifier was trained using k-1 subsets and was tested on the remaining subset. This procedure was repeated k times.

RESULTS
The mean age of the patients with TBI was 39.41 years and the majority of patients were male (up to 83%). Approximately 29% of the cases contained at least one missing value in a variable. Out of 2,381 cases analyzed in this study, only 1,682 (up to 71%) cases had full parameters; for the remainder of cases some value for some parameter was missing. After removing cases with missing values, we ended up with 1,682 cases. A summary of the data set is provided in Table 1. The distribution of each variable in both “favorable” and “unfavorable” groups is provided in Figure 1. In this figure, for the six variables of age, BS level, SBP on admission, GCS motor response, PT-INR, and Rotterdam index, within-group boxplots were provided. However, for the categorical variable “pupil reactivity,” for each category of anisocoria (A), brisk (B), and fixed (F) the proportion of favorable cases is calculated.

The results of the two employed feature selection methods, step-wise and random forest, are provided in Table 2 along with summaries of the most important features found by each
DISCUSSION

This work aimed to use machine learning techniques in developing a model to predict the 6-month clinical outcome using baseline parameters and brain-specific imaging parameters in severe TBI patients. The results shown in Table 3 and Figure 2 indicate that the three examined models performed well for this task. Statistical analyses of the performance of the developed methods showed that there is no significant difference between the estimation ability of the examined methods. However, the LR model can be preferred over the two other methods (i.e., SVM and RF) as it is simple and easily interpretable. Further, the model could be used to estimate the chance of un/favorable outcome for the patients; this could be more beneficial than estimating just the binary class label.

The predicted models were more accurate than other works [11,16] in predicting "unfavorable" outcomes. Our models also provided comparable AUC to several algorithms [23,24]. Moreover, the models presented in this paper compromised between specificity and sensitivity to yield a fair prediction for both groups at the same time. Nevertheless, the performance of a prediction model depends on the data used for training and testing the algorithm and it is hard to have a fair comparison between several models when the data is different and is not available. It should be noted that our goal was to achieve a balanced specificity and sensitivity using simple and easy-to-measure features provided at the early stage of hospitalization, while some previously developed algorithms [25] employed...
Figure 1. Boxplot for the six variables age, blood sugar (BS) level, systolic blood pressure (SBP) on admission, GCS motor response, coagulation measures prothrombin time-international normalized ratio (PT-INR), and Rotterdam index in “favorable” and “unfavorable” groups. For the categorical variable “pupil activity”, for category anisocoria (A), brisk (B), and fixed (F) the proportion of favorable cases is calculated individually.
features from physiological signals (e.g., electroencephalography) which are costly, computationally expensive, and hard to measure. More importantly, we examined interpretable machine learning algorithms (e.g., logistic regression) because for medical applications interpretability of the model is of the essence. Our results showed that by using a set of simple features and interpretable machine learning models trained on large data, it is possible to develop a reliable GOSE predictive model.

In terms of the parameters selected by the models, the three variables of “age,” “GCS motor response,” and “pupil reactivity” were found to be important by both feature selection models and were included in all the models; this finding is in line with previous works [11,16,17]. This result is consistent with the results provided in Figure 1. As shown, there is a shift in the average value between the GOSE categories for the two variables of “age” and “GCS motor response.” For the pupil reactivity, the majority (>76%) of cases with category brisk (B) or anisocoria (A) were “favorable” cases. SBP was included in the RF model which is consistent with clinical practice in which blood pressure assessment is part of treatment protocols for severe TBI patients. Besides, it was reported that low SBP before and during ICU intensive care unit admission are linked with high mortality rates in TBI patients. Overall, the parameters found by the RF are more consistent with clinical practice than the ones selected by SFS.

Figure 2. Mean receiver operating characteristic (ROC) curves and area under the curve (AUC) values for the prediction models developed for predicting unfavorable outcome after 6 months in the patients with severe traumatic brain injury. Values are presented as mean±standard error. LR: logistic regression; SVM: support vector machin; RF: random forest.

Figure 3. The relative importance of the variables used in random forest (RF)-based prediction model. The higher the value, the more important the feature is to the predicting model. GCS: Glasgow coma scale; F: fixed; B: brisk; BS: blood sugar; SPB: systolic blood pressure; PT-INR: prothrombin time-international normalized ratio.
To conduct an in-depth analysis of the role of features (variables) in predicting GOSE, we measured the importance of the parameters included in the predictor models. The feature importance for RFs was estimated using the Gini importance-based method. The average values of impurity decrease in the RF’s structure were computed for all the features as the feature importance. Additionally, we divided the non-numeric parameters, such as pupil and sex, into 0/1 bit parameters according to their unique values. The result is provided in Figure 3.

As shown, the “GCS motor response” is ranked as the most important feature. The value of importance of this parameter is > 0.3. The analysis also revealed that “pupil: F” is the second most important feature followed by age and BS. The results are in line with those provided in Figure 1. The box plots of the two variables “age” and “GCS motor response” indicate that there is a shift in the average values of these two variables between the group with “favorable” GOSE and “unfavorable” GOSE. For the categorical variable “pupil reactivity,” the majority (>76%) of cases with brisk pupillary response were “favorable” cases. Normally, pupils react to light briskly. However, patients with increased intracranial pressure may show sluggish or slow pupillary response. Fixed (nonreactive) pupils are in general associated with severe brain damage or high intracranial pressure value which is consistent with our results in Figure 1; approximately 65% of cases with fixed pupil activity belonged to the “unfavorable” category. In short, in-depth analysis of the effect of the variable in predicting GOSE revealed that the three parameters of “GCS motor response,” “pupil activity,” and “age” are the more important factors in predicting GOSE 6-month outcome in TBI patients.

This study showed that machine learning models when trained using a large data set could be used to predict the 6-month outcome in TBI patients using the parameters measured at admission. Our findings showed that the logistic regression model is superior to SVM and RF models because it is simple, more interpretable, and as accurate as the two more complicated models of SVM and RF. These promising results provide early evidence on the capability of machine learning models in predicting outcomes in TBI patients and ultimately assist physicians as possible decision support tools in diagnosing, optimizing treatment procedures, improving clinical outcomes, and offering substantial economic savings.

**CONFLICT OF INTEREST**

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

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Association between the National Health Insurance coverage benefit extension policy and clinical outcomes of ventilated patients: a retrospective study

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Background: This study aimed to investigate the association between the Korean National Health Insurance coverage benefit extension policy and clinical outcomes of patients who were ventilated owing to various respiratory diseases.

Methods: Data from 515 patients (male, 69.7%; mean age, 69.8±12.1 years; in-hospital mortality rate, 28.3%) who were hospitalized in a respiratory intensive care unit were retrospectively analyzed over 5 years.

Results: Of total enrolled patients, 356 (69.1%) had one benefit items under this policy during their hospital stay. They had significantly higher medical expenditure (total: median, 23,683 vs. 12,742 U.S. dollars [USD], P<0.001), out-of-pocket (median, 5,932 vs. 4,081 USD; P<0.001), and a lower percentage of out-of-pocket medical expenditure relative to total medical expenditure (median, 26.0% vs. 32.2%; P<0.001). Patients without benefit items associated with higher in-hospital mortality (hazard ratio [HR], 2.794; 95% confidence interval [CI], 1.980–3.941; P<0.001). In analysis of patients with benefit items, patients with three items (“cancer,” “tuberculosis,” and “disability”) had significantly lower out-of-pocket medical expenditure (3,441 vs. 6,517 USD, P<0.001), and a lower percentage of out-of-pocket medical expenditure relative to total medical expenditure (17.2% vs. 27.7%, P<0.001). They were associated with higher in-hospital mortality (HR, 3.904; 95% CI, 2.533–6.039; P<0.001).

Conclusions: Our study showed patients with benefit items had more medical resources and associated improved in-hospital survival. Patients with the aforementioned three benefit items had lower out-of-pocket medical expenditure due to the implementation of this policy, but higher in-hospital mortality.

Key Words: health expenditures; health insurance; mechanical ventilators; mortality

INTRODUCTION

Patients receiving mechanical ventilation (MV) require various medical resources for a long period of time in an intensive care unit (ICU). In addition, advances in the management of acute critical care intervention have led to improvement of survival, which is associated with
high medical costs. As a result, high out-of-pocket medical expenditures place a severe financial burden on the families or surrogates of patients.

To address the financial burden of healthcare, the National Health Insurance (NHI) System was implemented in the Republic of Korea (hereafter called Korea) in 1977 [1]. In this system, the NHI program is a social insurance benefit scheme that covers the whole population [1-3]. In addition to this insurance program, the Korean government has introduced a health insurance benefit extension policy targeting the elderly, pregnant women and newborns, Medicare recipients, and individuals with severe illnesses, malignancies, and rare incurable diseases for payment relief [4]. The benefit items and associated benefit rules under this policy have been implemented, including extensions of benefit period, and improvements of the medical reimbursement systems. This policy has been expanded to provide medical assistance without causing patients severe financial difficulties.

As a result of improvements in critical care medicine, many patients receiving ventilator care require various medical resources for a long time in an ICU, which is associated with high medical expenditures. In the present study, we hypothesized that the expansion of benefit items and revision of associated rules under this policy have been implemented, including extensions of benefit period, and improvements of the medical reimbursement systems. This policy has been expanded to provide medical assistance without causing patients severe financial difficulties.

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MATERIALS AND METHODS

Study Design and Patient Selection

This retrospective, observational study was conducted in the 12-bed adult respiratory ICU of a regional center for respiratory diseases that was established in December 2015. This center is located in a 1,200-bed university-affiliated tertiary care hospital. The respiratory ICU has full cardiovascular facilities and close airway monitoring equipment, with the nurse-to-bed ratio is 1:3. All subjects were managed according to therapeutic recommendations based on a lung-protective ventilator strategy [5].

Data from patients who were admitted to the respiratory ICU between December 1, 2015, and November 30, 2020, were retrospectively evaluated. The survival status of all patients was obtained until March 10, 2021. All adult subjects (≥18 years of age) admitted to ICU were assessed for eligibility. Patients who required ventilator care for more than 24 hours and who required ventilator care primarily due to respiratory diseases were included. Medical Aid (MA) beneficiaries were excluded because MA provides healthcare benefits to low-income families and sets an upper limit for out-of-pocket medical expenditure based on the National Basic Living Security Act [6,7]; the NHI benefit extension policy would be little effect on clinical outcomes in these patients. Patients were also excluded if they had not received ventilator care, had other minor types of insurance such as automobile insurance and industrial accident compensation insurance, had no insurance, or information about their insurance was lacking. Private insurance programs were not analyzed in this study (Figure 1).

The relevant medical, laboratory, and radiologic data were extracted and used to fill out a case report form for each patient. These data were then analyzed. The study protocol was approved by the Institutional Review Board of Pusan National University Hospital (IRB No. 2104-010-101). Owing to the observational nature of the study, the need for informed consent from enrolled subjects or their families or surrogates was waived. This study had no impact on the treatment of the enrolled patients.

Data Collection

Demographic and clinical data, including age, sex, body mass index, length of stay (LOS) in the ICU and hospital, and duration of MV, were retrospectively obtained from the electronic medical records (EMRs) of each subject. Illness severity was
measured using the Acute Physiology and Chronic Health Evaluation (APACHE) II score, and accompanying organ failure was assessed using the Sequential Organ Failure Assessment (SOFA) score [8,9]. The APACHE II and SOFA scores were calculated from laboratory and clinical data obtained within the first 24 hours of ICU admission. On admission, the underlying comorbidities of all enrolled subjects were gathered from EMRs. In addition, to determine concurrent comorbidities prior to admission, Charlson’s weighted index of comorbidities (WIC) was evaluated from EMRs [10]. The primary reason for ventilator care at the time of ICU admission, and whether attending physicians discussed life-sustaining therapy (withdrawing or withholding ICU care) with patients’ families or surrogates were also evaluated from the medical records. ICU and in-hospital mortality after ICU admission was assessed. The primary outcome measure was in-hospital mortality.

To evaluate the association between medical expenditure per patient and clinical outcomes, total and out-of-pocket medical expenditure for all medical resources (including all medicines) during the hospital (ICU and general ward) stay was retrieved from the EMRs of each subject with the permission of the IRB. Expenditure is presented in U.S. dollars (USD) using an exchange rate of 1 USD equaling 1,140.10 Korean won (exchange rate on March 10, 2021). Also, the main applicable benefit items under the NHI benefit extension policy to reduce each patient’s out-of-pocket medical expenditure during their hospital stay were evaluated.

**Statistical Analysis**
Continuous variables are expressed as the mean±standard deviation (SD) if they had a normal distribution, or median with interquartile range. The Student t-test and Wilcoxon rank-sum test were used to compare continuous variables with a normal distribution and variables with a non-normal distribution, respectively. Categorical variables are expressed as numbers (percentages) and were compared using the chi-square test or Fisher’s exact test (for small numbers), as applicable. Pearson’s correlation coefficient (γ) was calculated to evaluate the relationship between medical expenditure (total and out-of-pocket) per person and LOS (in the hospital and ICU). Univariate proportional hazard models were developed to determine the relationship between healthcare insurance benefit items and in-hospital mortality. Variables with P<0.10 were included in multivariate Cox proportional hazard models. Hazard ratios with 95% confidence intervals are reported. Kaplan-Meier estimates of in-hospital mortality were stratified according to health insurance benefit items status, and curves were compared using log-rank test. All tests were two-tailed, and P-values <0.05 were considered statistically significant. All analyses were performed using the language R (http://cran.r-project.org) version 4.0.5, and additional packages (survival).

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**Figure 1.** Flowchart of patient selection and clinical course.
RESULTS

Characteristics of Total Patients
During the study period, 924 patients were admitted to respiratory ICU. After application of exclusion criteria, 515 patients were eligible for participation (Figure 1). Their ICU and in-hospital mortality rate was 22.9% and 28.3%, respectively. The most common diagnosis leading to MV was pneumonia (87.2%). Chronic lung diseases (such as chronic obstructive pulmonary disease, interstitial lung disease, and destroyed lung caused by various origins) were the most common underlying diseases. The median total and out-of-pocket medical expenditures during hospital stays were 19,986 (range, 2,560–573,591) and 5,319 (range, 703–134,199) USD, respectively. The median percentage of out-of-pocket medical expenditure relative to total medical expenditure was 28.3% (range, 8.3%–86.3%). There was a positive correlation between medical expenditure (total and out-of-pocket) and hospital LOS ($\gamma=0.944$, $P<0.001$ and $\gamma=0.875$, $P<0.001$, respectively). In total, 356 (69.1%) of NHI beneficiaries had benefit items under the NHI benefit extension policy.

Comparisons between Patients with and without Benefit Items under Health Insurance Benefit Extension Policy
The clinical characteristics of patients with and without benefit items are compared in Table 1. Patients with benefit items had a significantly longer hospital and ICU LOS, higher medical expenditure (total and out-of-pocket), a lower percentage of out-of-pocket medical expenditure, and a lower in-hospital mortality rate. Values are presented as number (%), mean±standard deviation, or median (interquartile range). BMI: body mass index; ICU: intensive care unit; LOS: length of stay; MV: mechanical ventilation; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; USD: U.S. dollars.

Table 1. Clinical characteristics of total patients and comparisons between with and without National Health Insurance benefit items

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n=515)</th>
<th>Health insurance benefit item</th>
<th>P-valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n=356)</td>
<td>No (n=159)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>359 (69.7)</td>
<td>256 (71.9)</td>
<td>0.128</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>69.8±12.1</td>
<td>69.3±12.2</td>
<td>0.149</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.5±4.8</td>
<td>21.6±4.6</td>
<td>0.356</td>
</tr>
<tr>
<td>ICU LOS (day)</td>
<td>11 (6–18)</td>
<td>12 (7–19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MV LOS (day)</td>
<td>9 (4–18)</td>
<td>11 (5–19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospital LOS (day)</td>
<td>25 (13–45)</td>
<td>31 (19–53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>APACHE II scoreb</td>
<td>21.6±6.7</td>
<td>21.5±6.4</td>
<td>0.893</td>
</tr>
<tr>
<td>SOFA scoreb</td>
<td>7.7±3.1</td>
<td>7.6±2.9</td>
<td>0.111</td>
</tr>
<tr>
<td>Main diagnosis leading to MV: pneumonia</td>
<td>449 (87.2)</td>
<td>309 (86.8)</td>
<td>0.802</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>196 (38.1)</td>
<td>137 (38.5)</td>
<td>59 (37.1)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>175 (34.0)</td>
<td>127 (35.7)</td>
<td>48 (30.2)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>163 (31.7)</td>
<td>111 (31.2)</td>
<td>52 (32.7)</td>
</tr>
<tr>
<td>Chronic neurological disease</td>
<td>152 (29.5)</td>
<td>104 (29.2)</td>
<td>48 (30.2)</td>
</tr>
<tr>
<td>Solid malignant tumor</td>
<td>96 (18.6)</td>
<td>77 (21.6)</td>
<td>19 (11.9)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>57 (11.1)</td>
<td>45 (12.6)</td>
<td>12 (7.5)</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>38 (7.4)</td>
<td>34 (9.6)</td>
<td>4 (2.5)</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>23 (4.5)</td>
<td>15 (4.2)</td>
<td>8 (5.0)</td>
</tr>
<tr>
<td>Hematological malignancy</td>
<td>5 (1.0)</td>
<td>4 (1.1)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Total medical expenditures (USD)c</td>
<td>19,986 (11,959–32,104)</td>
<td>23,683 (15,098–36,597)</td>
<td>12,742 (8,790–22,118)</td>
</tr>
<tr>
<td>Out-of-pocket medical expenditures (USD)c</td>
<td>5,319 (3,136–8,488)</td>
<td>5,932 (3,421–8,801)</td>
<td>4,081 (2,717–7,268)</td>
</tr>
<tr>
<td>Ratio of out-of-pocket for total medical expenditures (%)</td>
<td>28.3 (22.0–32.6)</td>
<td>26.0 (18.8–30.2)</td>
<td>32.2 (28.6–35.9)</td>
</tr>
<tr>
<td>Tracheostomy at hospital discharge</td>
<td>308 (59.8)</td>
<td>238 (66.9)</td>
<td>70 (44.0)</td>
</tr>
<tr>
<td>Discussion with attending physicians about withdrawing or withholding life-sustaining treatment</td>
<td>168 (32.6)</td>
<td>99 (27.8)</td>
<td>69 (43.8)</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>146 (28.3)</td>
<td>88 (24.7)</td>
<td>58 (36.5)</td>
</tr>
</tbody>
</table>

Values are presented as number (%), mean±standard deviation, or median (interquartile range).

BMI: body mass index; ICU: intensive care unit; LOS: length of stay; MV: mechanical ventilation; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; USD: U.S. dollars.

aComparisons between patients with and without health insurance benefit items; bAll clinical data were calculated or obtained from medical records on the day of ICU admission; cTotal and out-of-pocket medical expenditure for all medical resources used (including all medicines) during ICU and general ward stays was retrieved.
of-pocket medical expenditure relative to total medical expenditure, and lower in-hospital mortality than patients without benefit items.

Comparisons of Clinical Outcomes According to Benefit Items under Health Insurance Benefit Extension Policy
Nine benefit items were applied to NHI beneficiaries, and the most common benefit item was “long-term hospitalization” (Figure 2). Patients with three benefit items (“cancer,” “tuberculosis,” and “disability” categorized as group A) had significantly higher in-hospital mortality than patients with other benefit items (categorized as group B). Patients with these benefit items had significantly higher APACHE II and SOFA scores, a higher Charlson’s WIC, and a lower percentage of out-of-pocket medical expenditure relative to total medical expenditure. Furthermore, families or surrogates of patients with these benefit items had significantly more discussions with their attending physicians about life-sustaining therapy (Table 2).

Association between Healthcare Insurance Benefit Items and In-hospital Mortality
Univariate and multivariate Cox regression were constructed to evaluate the association between healthcare insurance benefit items and in-hospital mortality in total enrolled patients (Table 3). We found patients without benefit items were significantly associated with higher in-hospital mortality. The Kaplan-Meier estimate of survival was consistent with a survival benefit of benefit items (Figure 3A). In further analysis of patients with benefit items, Group A showed a significant association with higher in-hospital mortality. Also, the Kaplan-Meier estimate of survival was consistent with a survival benefit of group B (Figure 3B).

DISCUSSION
The present study evaluated the association between the NHI benefit extension policy and clinical outcomes of NHI beneficiaries requiring ventilator care owing to respiratory diseases. Furthermore, we investigated the differences of clinical outcomes according to various benefit items. To our knowledge, this is the first study to analyze the clinical characteristics and outcomes of ventilated patients under this policy in Korea.

We found that about 70% of total enrolled patients were eligible for one benefit during their hospital stay, and these patients used more medical resources, reflected by total medical expenditures, and their in-hospital mortality was lower than that of patients who were ineligible for benefits. Our findings

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Figure 2. Benefit items under the health insurance benefit extension policy and medical expenditure. aThe secondary poor is a class of people who are economically similar to or slightly better off than the poor. They are potentially poor, but cannot receive some benefits available to Medical Aid beneficiaries because their income exceeds the minimum cost of living due to their ability to work and they have some fixed property.
Table 2. Comparison of clinical characteristics according to benefit items under health insurance benefit extension policy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Health insurance benefit item</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A (n=73)</td>
<td>Group B (n=283)</td>
</tr>
<tr>
<td>Male</td>
<td>59 (80.8)</td>
<td>197 (69.6)</td>
</tr>
<tr>
<td>Age ≥65 yr</td>
<td>49 (67.1)</td>
<td>217 (76.7)</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>22.9±6.8</td>
<td>21.2±6.3</td>
</tr>
<tr>
<td>SOFA score</td>
<td>8.6±2.9</td>
<td>7.3±2.9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.1±3.7</td>
<td>21.8±4.3</td>
</tr>
<tr>
<td>Main diagnosis leading to MV: pneumonia</td>
<td>58 (79.5)</td>
<td>251 (88.7)</td>
</tr>
<tr>
<td>Charlson’s WIC</td>
<td>3.4±1.8</td>
<td>2.7±1.8</td>
</tr>
<tr>
<td>Tracheostomy at hospital discharge</td>
<td>39 (53.4)</td>
<td>199 (70.3)</td>
</tr>
<tr>
<td>ICU LOS</td>
<td>11 (5–19)</td>
<td>12 (8–19)</td>
</tr>
<tr>
<td>MV LOS</td>
<td>11 (4–18)</td>
<td>11 (5–19)</td>
</tr>
<tr>
<td>Hospital LOS</td>
<td>24 (13–54)</td>
<td>33 (21–53)</td>
</tr>
<tr>
<td>Total medical expenditure (USD)</td>
<td>21,036 (12,554–34,026)</td>
<td>23,772 (15,446–36,622)</td>
</tr>
<tr>
<td>Out-of-pocket medical expenditure (USD)</td>
<td>3,441 (2,254–7,139)</td>
<td>6,517 (4,263–9,602)</td>
</tr>
<tr>
<td>Out-of-pocket medical expenditure relative to total medical expenditure (%)</td>
<td>17.2 (13.7–21.0)</td>
<td>27.7 (21.9–31.1)</td>
</tr>
<tr>
<td>Discussion with attending physicians about withdrawing or withholding life-sustaining treatment</td>
<td>41 (56.2)</td>
<td>58 (20.5)</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>40 (54.8)</td>
<td>48 (17.0)</td>
</tr>
</tbody>
</table>

Values are presented as number (%), mean±standard deviation, or median (interquartile range). Group A includes following benefit items: cancer, tuberculosis and disability. Group B includes following benefit items: long-term hospitalization, rarely incurable, secondary poor, secondary poor with disability, hemodialysis, and severely ill.

APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; BMI: body mass index; MV: mechanical ventilation; WIC: weighted index of comorbidities; ICU: intensive care unit; LOS: length of stay; USD: U.S. dollars.

All clinical data were calculated or obtained from medical records on day of ICU admission; Total and out-of-pocket medical expenditures for all medical resources used (including all medicines) during ICU and general ward stay were retrieved.

Figure 3. Kaplan-Meier curves of survival curves of in-hospital survival after intensive care unit admission according to the presence or absence of health insurance benefit items in total enrolled patients (Log-rank, 37.7; P<0.001) (A) and according to categorized as group A or B in patients with health insurance benefit items (Log-rank, 46.3; P<0.001) (B). Group A includes following benefit items: cancer, tuberculosis and disability. Group B includes following benefit items: long-term hospitalization, rarely incurable, secondary poor, secondary poor with disability, hemodialysis, and severely ill.
suggest that the health insurance benefit range of this policy should be adjusted so that ventilated patients can effectively receive quality healthcare services without facing any financial burden because universal healthcare coverage is also a key concern of critically ill patients [4,11]. Furthermore, it would be necessary for critical care physicians to consider the benefit items and out-of-pocket medical expenditure of patients when discussing future treatment planning with their families or surrogates.

In further analyses of patients with benefit items, clinical characteristics and outcomes differed according to benefit items under this policy. Although patients with group A benefit items received significant financial benefits, reflected by a significantly lower percentage of out-of-pocket medical expenditure relative to total medical expenditure than patients with group B benefit items, they had significantly more severe illness and accompanying organ failure at ICU admission and higher in-hospital mortality. Our study indicates that simply reducing out-of-pocket expenditure by implementing this policy would not markedly affect the survival of these patients.

In our study, we tried to investigate whether the NHI benefit extension policy and benefit items under this policy were useful prognostic indicators. For assessing prognosis, various clinical and demographic indicators should be considered, however, we could not comprehensively do this because our study had a single-center retrospective design and included a small number of patients. Furthermore, the present study indicates in-hospital mortality differed according to benefit items and associated benefit rule. In particular, the clinical outcomes of patients with the benefit item “cancer (solid and hematologic malignancies)” differ depending on the type and stage. Therefore, additional studies including a large number of patients are needed to determine whether each benefit item under this policy would be a valuable prognostic indicator in critical ill ventilated patients.

Our study has several limitations. First, we hypothesized the family support and socioeconomic status of each patient would be associated with clinical outcomes, however, we could not evaluate this because our study had an observational retrospective design. Second, we investigated the effect of the NHI benefit extension policy on patients requiring ventilation due to respiratory diseases. However, the relationships between this policy and clinical outcomes may differ in patients requiring ventilation for other reasons. Further studies of heterogeneous populations are needed to evaluate the effect of this policy on clinical outcomes. Finally, this study was performed in one hospital, and the sample size was small; therefore, our results may not represent the general situation in Korea. However, considering that our institution is one of the best-equipped hospitals in our country, and that the health insurance benefit expansion policy and associated benefit rules apply across Korea, the situation in other Korean hospitals is likely similar to that in our hospital.

In conclusion, analysis of the Korean NHI coverage benefit extension policy in ventilated patients showed that this policy increased the use of medical resources and associated improved in-hospital mortality of NHI beneficiaries. Furthermore, the percentage of out-of-pocket medical expenditure relative to total medical expenditure and in-hospital mortality differed according to benefit items under this policy. Large-

| Table 3. Univariate and multivariate analysis of factors associated with in-hospital mortality in total patients and subjects with health insurance benefit items |
|--------------------------------------------------|-----------------|-----------------|-----------------|
| Factor                                           | Univariate analysis | Multivariate analysis |
|                                                  | HR (95% CI)       | P-value          | HR (95% CI)     | P-value |
| Total patients                                   |                  |                  |                  |         |
| Patients without health insurance benefit items  | 2.805 (1.993–3.947) | <0.001         | 2.794 (1.980–3.941) | <0.001 |
| SOFA score²                                     | 1.175 (1.112–1.241) | <0.001         | 1.138 (1.068–1.212) | <0.001 |
| Age ≥65 yr                                      | 1.465 (0.958–2.242) | 0.078          |                  |         |
| Patients with health insurance benefit items²   |                  |                  |                  |         |
| Group A                                          | 3.951 (2.583–6.045) | <0.001         | 3.904 (2.533–6.039) | <0.001 |
| SOFA score²                                     | 1.107 (1.028–1.192) | 0.007          |                  |         |

Statistical significance was tested by univariate Cox proportional hazards models and multivariate Cox hazards models.

HR: hazard ratio; CI: confidence interval; SOFA: Sequential Organ Failure Assessment.
²All clinical data was calculated or checked from; ²²Patients were divided into two groups (group A includes following benefit items: cancer, tuberculosis and disability. Group B includes following benefit items: long-term hospitalization, rarely incurable, secondary poor, secondary poor with disability, hemodialysis, and severely ill).
scale multicenter studies are required to determine the effect of this policy on clinical outcomes of patients requiring ventilator care due to reasons other than respiratory diseases.

CONFLICT OF INTEREST

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

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AUTHOR CONTRIBUTIONS

Conceptualization: WY, KL. Data curation: all authors. Formal analysis: WY, KL. Funding acquisition: KL. Methodology: WY, KL. Project administration: WY, KL. Visualization: WY, KL. Writing—original draft: WY, KL. Writing—review & editing: KL.

REFERENCES


Nosocomial meningitis in intensive care: a 10-year retrospective study and literature review

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Background: Nosocomial meningitis is a medical emergency that requires early diagnosis, prompt initiation of therapy, and frequent admission to the intensive care unit (ICU).

Methods: A retrospective study was conducted in adult patients diagnosed with nosocomial meningitis who required admission to the ICU between April 2010 and March 2020. Meningitis/ventriculitis and intracranial infection were defined according to Centers for Disease Control and Prevention guidelines.

Results: An incidence of 0.75% of nosocomial meningitis was observed among 70 patients. The mean patient age was 59 years and 34% were ≥65 years. Twenty percent of patients were in an immunocompromised state. A clear predisposing factor for nosocomial meningitis (traumatic brain injury, basal skull fracture, brain hemorrhage, central nervous system [CNS] invasive procedure or device) was present in 93% of patients. Fever was the most frequent clinical feature. A microbiological agent was identified in 30% of cases, of which 27% were bacteria, with a predominance of Gram-negative over Gram-positive. Complications developed in 47% of cases, 24% of patients were discharged with a Glasgow coma scale <14, and 37% died. There were no clear clinical predictors of complications. Advanced age (≥65 years old) and the presence of complications were associated with higher hospital mortality.

Conclusions: Nosocomial meningitis in critical care has a low incidence rate but high mortality and morbidity. In critical care patients with CNS-related risk factors, a high level of suspicion for meningitis is warranted, but diagnosis can be hindered by several confounding factors.

Key Words: bacterial meningitis; central nervous system infections; critical care; critical illness; healthcare-associated meningitis; hospital infection

INTRODUCTION

Central nervous system (CNS) infections are medical emergencies that require an early diagnosis, prompt initiation of therapy, and frequent admission to an intensive care unit (ICU) [1]. Nosocomial meningitis causes 40% of cases of bacterial meningitis in industrialized countries [2] and is associated with high mortality and morbidity [1]. Risk factors include invasive procedures (such as craniotomy, internal ventricular catheters, external ventricular drains (EVD),
Valdoleiros SR, et al. 
Nosocomial meningitis in intensive care

external lumbar catheters, and lumbar puncture) [3-5], moderate or severe head trauma [6-8], subarachnoid hemorrhage [9,10], and, in rare cases, metastatic infection in patients with bacteremia [4]. Tumor neurosurgery, severe traumatic brain injury (TBI), and subarachnoid hemorrhage carry the highest risk for postoperative meningitis [2]. Possible clinical characteristics of nosocomial meningitis include fever, headache onset, nausea, change in mental status, evidence of meningeal irritation, and seizures [11]. Nevertheless, diagnosing nosocomial meningitis is challenging and particularly problematic in the ICU.

Patients in ICUs are often sedated or unresponsive due to other conditions or underlying neurologic diseases, which impairs clinical assessment. Additionally, fever or increase in acute phase proteins can have several potential foci, infectious or non-infectious, including injury to the thermoregulation center [12]. Infections associated with cerebrospinal fluid (CSF) shunts can cause nonspecific symptoms such as general malaise or low-grade fever [4]; signs of meningeal irritation are present in less than 50% of patients. [4]

On the other hand, CSF biochemical profiles can be drastically altered by intracerebral hemorrhage, immunosuppression [12], and local inflammatory reactions to blood breakdown products or chemicals after neurosurgical interventions (expected presence of elevated proteinorrachia and pleocytosis [13]). A previous study revealed that the CSF characteristics in post-neurosurgical patients were similar between aseptic meningitis and bacterial meningitis cases, including glucose level [13]. In patients with EVD, severe disturbances in the CSF limit the value of CSF analysis for prediction or diagnosis of EVD-related meningitis [14]. Frequent prior or concomitant use of antimicrobials in the ICU further complicates interpretation of the CSF tests; although cell counts in CSF are useful, they have low sensitivity and specificity in some clinical subgroups [14].

CSF culture is considered the gold standard for diagnosing bacterial meningitis. However, its clinical use in ICU populations is limited by frequent prior antibiotic administration, which decreases culture yield. Infections that require immediate therapeutic attention must be differentiated from contamination or device colonization [12]. In up to 70% of meningitis cases that develop after intraventricular hemorrhage, meningitis is aseptic [13].

To assess the impact of nosocomial meningitis in intensive care patients, a retrospective study was conducted. Aims included estimating disease incidence and identifying risk factors for worse outcomes.

**KEY MESSAGES**

- Nosocomial meningitis in critical care has a low incidence rate but high mortality and morbidity.
- In this retrospective study of nosocomial meningitis, fever was the most frequent clinical sign.
- Advanced age and complications were associated with higher mortality.

**MATERIALS AND METHODS**

This study was approved by the Ethics Committee and by the Administrative Council of CHUPorto (No. 2019.317). Individual informed consent was waived.

In this retrospective, single-center study, we reviewed all adult patients (over 18 years of age) diagnosed with nosocomial meningitis who were admitted to the ICU at University Hospital Center of Porto–CHUPorto between April 2010 and March 2020. CHUPorto is a central and university teaching hospital (in association with the University of Porto) with over 800 beds, 24 of which are ICU beds. The hospital admits 35,000 patients per year. As a tertiary center, it serves a population of over 3,000,000 people.

Meningitis, ventriculitis, and intracranial infection were defined according to the guidelines of Centers for Disease Control and Prevention (CDC) (Supplementary Table 1) [15]. Infection acquisition was considered nosocomial when it occurred at least 48 hours after admission. Altered mental status was defined as not being alert on “alert, verbal, pain, unresponsive (AVPU)” score or by a Glasgow coma scale (GCS) score <14 points.

Statistical analyses were performed with IBM SPSS ver. 26 (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test of normality was used to assess whether continuous variables had a normal or non-normal distribution; Student t-test and the Mann-Whitney U-test were performed accordingly. To compare categorical variables, Fisher’s exact test and chi-square test were applied. The presence of complications, non-alert state at discharge (“AVPU” score), and mortality were established outcomes. Univariate and multivariate analyses were performed to assess the associations of significant variables with hospital and 30-day mortalities. Statistical significance was accepted at P<0.05.
RESULTS

Descriptive Analysis

Between April 2010 and March 2020, 10,664 adult patients were admitted to the ICU; of these, 80 had a diagnosis of nosocomial meningitis (0.75%). Ten patients were excluded from the study due to insufficient data or because they did not fulfill the diagnostic criteria for CNS infection (Figure 1).

Study population characteristics are presented in Table 1. The population had a mean age of 59±16 years (range, 18–88), with a large proportion (34.3%) of elderly patients (≥65 years old). The population was predominantly male (62.9%). Predisposing underlying conditions included alcohol abuse (n=13, 18.6%), diabetes mellitus (n=9, 12.9%), immunosuppressive therapy (n=3, 4.3%), primary immunodeficiency (n=1, 1.4%), and drug abuse (n=1, 1.4%).

Of the 70 included patients, 69 met the diagnostic criteria for meningitis/ventriculitis and one for intracranial infection with meningitis (Figure 1). Sixty-five patients (93%) had a clear CNS-related predisposing factor for nosocomial meningitis (TBI, basal skull fracture, brain hemorrhage, or CNS invasive procedure); of the five remaining patients (7.1%), two had bacteremia, one had endocarditis, and one had a dental abscess. Invasive CNS procedure was the most common risk factor for nosocomial meningitis (n=62, 88.6%).

Clinical and laboratory characteristics of CNS infection are depicted in Table 2. Fever was the most common clinical feature, occurring in 90% of patients. Seizures and new focal deficits (hemiparesis) were observed in 11 (15.7%) and five (7.1%) patients, respectively. Among non-sedated patients (n=38), altered mental status (defined as not alert on AVPU score or GCS <14 points) was the second most frequent symptom (n=27).

Lumbar puncture was performed in most patients. CSF analysis disclosed a mean glucose level of 0.69±0.35 g/L, median protein of 1.15 g/L (interquartile range [IQR], 0.65–1.84), and median white cell count of 359/μL (IQR, 132–1,634) (Table 2).

Table 1. Patients’ characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>59±16</td>
</tr>
<tr>
<td>Age ≥65 yr</td>
<td>24 (34.3)</td>
</tr>
<tr>
<td>Male</td>
<td>44 (62.9)</td>
</tr>
<tr>
<td>Functional status: independent</td>
<td>64 (91.4)</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
</tr>
<tr>
<td>Immunosuppressive therapy</td>
<td>3 (4.3)</td>
</tr>
<tr>
<td>Primary immunodeficiency</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td>Type 2, insulin-treated</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Type 2, non-insulin-treated</td>
<td>7 (10.0)</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>13 (18.6)</td>
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<tr>
<td>Drug abuse</td>
<td>1 (1.4)</td>
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<td>Predisposing condition</td>
<td></td>
</tr>
<tr>
<td>TBI</td>
<td>24 (34.3)</td>
</tr>
<tr>
<td>Basal skull fracture</td>
<td>7 (10.0)</td>
</tr>
<tr>
<td>CNS invasive procedure</td>
<td>62 (88.6)</td>
</tr>
<tr>
<td>Craniotomy</td>
<td>31 (44.3)</td>
</tr>
<tr>
<td>Craniectomy</td>
<td>17 (24.3)</td>
</tr>
<tr>
<td>Cranioplasty</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Spinal surgery</td>
<td>4 (5.7)</td>
</tr>
<tr>
<td>CNS invasive device</td>
<td>45 (64.3)</td>
</tr>
<tr>
<td>EVD</td>
<td>23 (32.8)</td>
</tr>
<tr>
<td>ICP-monitoring catheter</td>
<td>32 (45.7)</td>
</tr>
<tr>
<td>Lumbar drain</td>
<td>4 (5.7)</td>
</tr>
<tr>
<td>Distant focus of infection</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Odontogenic abscess</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>1 (1.4)</td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation or number (%). TBI: traumatic brain injury; CNS: central nervous system; EVD: external ventricular drain; ICP: intracranial pressure.
Table 2. Clinical and laboratory characteristics of CNS infection

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sign and symptom</strong></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>63 (90)</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>4 (5.7)</td>
</tr>
<tr>
<td>Meningism</td>
<td>3 (4.3)</td>
</tr>
<tr>
<td>Seizure</td>
<td></td>
</tr>
<tr>
<td>Seizure</td>
<td></td>
</tr>
<tr>
<td>Partial seizures</td>
<td>11 (15.7)</td>
</tr>
<tr>
<td>Non-convulsive status epilepticus</td>
<td>6 (8.6)</td>
</tr>
<tr>
<td>Generalized tonic-clonic seizures</td>
<td>4 (5.7)</td>
</tr>
<tr>
<td>Non-sedated patient</td>
<td>3 (4.3)</td>
</tr>
<tr>
<td>Headache</td>
<td>38 (54.3)</td>
</tr>
<tr>
<td>Behavior change</td>
<td>6 (8.6)</td>
</tr>
<tr>
<td>New focal deficits</td>
<td>5 (7.1)</td>
</tr>
<tr>
<td>&quot;AVPU&quot; at diagnosis</td>
<td></td>
</tr>
<tr>
<td>Alert</td>
<td>11 (15.7)</td>
</tr>
<tr>
<td>Responsive to verbal stimuli</td>
<td>4 (5.7)</td>
</tr>
<tr>
<td>Responsive to pain</td>
<td>15 (21.4)</td>
</tr>
<tr>
<td>Unresponsive</td>
<td>8 (11.4)</td>
</tr>
<tr>
<td>Glasgow coma score at diagnosis</td>
<td></td>
</tr>
<tr>
<td>3–8 points</td>
<td>13 (18.6)</td>
</tr>
<tr>
<td>9–13 points</td>
<td>15 (21.4)</td>
</tr>
<tr>
<td>14–15 points</td>
<td>8 (11.4)</td>
</tr>
<tr>
<td><strong>Timing of symptoms and diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>Time between hospital admission and diagnosis</td>
<td>10.9±8.6 (1–48)</td>
</tr>
<tr>
<td>Time until readmission</td>
<td>9.2±4.6 (2–13)</td>
</tr>
<tr>
<td>Time between any predisposing factor and signs/symptoms</td>
<td>6.7±5.8 (0–25)</td>
</tr>
<tr>
<td>Time between TBI and signs/symptoms</td>
<td>6.6±6.5 (2–34)</td>
</tr>
<tr>
<td>Time between basal skull fracture and signs/symptoms</td>
<td>6.2±4.2 (2–12)</td>
</tr>
<tr>
<td>Time between CNS invasive procedure and signs/symptoms</td>
<td>6.5±5.6 (0–25)</td>
</tr>
<tr>
<td>Time between CNS invasive device and signs/symptoms</td>
<td>5.5±6.0 (0–41)</td>
</tr>
<tr>
<td>Time between symptoms and diagnosis</td>
<td>2.0±2.1 (0–10)</td>
</tr>
<tr>
<td>Time between any predisposing factor and diagnosis</td>
<td>9.0±7.5 (2–43)</td>
</tr>
<tr>
<td>Time between TBI and diagnosis</td>
<td>8.9±6.5 (2–37)</td>
</tr>
<tr>
<td>Time between basal skull fracture and diagnosis</td>
<td>7.3±4.2 (2–13)</td>
</tr>
<tr>
<td>Time between CNS invasive procedure and diagnosis</td>
<td>8.7±6.1 (2–29)</td>
</tr>
<tr>
<td>Time between CNS invasive device and diagnosis</td>
<td>7.4±6.2 (0–43)</td>
</tr>
<tr>
<td><strong>Blood panel</strong></td>
<td></td>
</tr>
<tr>
<td>White cell count (×10^3/mm^3)</td>
<td>11,690±5,516 (980–27,660)</td>
</tr>
<tr>
<td>Neutrophils (×10^3/mm^3)</td>
<td>9,226±4,572 (630–22,740)</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>127±93 (13–493)</td>
</tr>
<tr>
<td>Procalcitonin (ng/ml)</td>
<td>0.24 (0.17–0.78)</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>2.9±0.46 (1.65–4.00)</td>
</tr>
<tr>
<td><strong>CSF analysis</strong></td>
<td></td>
</tr>
<tr>
<td>Glucose (g/L)</td>
<td>0.69±0.35 (0.01–1.45)</td>
</tr>
<tr>
<td>Protein (g/L)</td>
<td>1.15 (0.65–1.84)</td>
</tr>
<tr>
<td>Red cell (×10^12/l)</td>
<td>24,300 (2,350–89,500)</td>
</tr>
<tr>
<td>White cell (×10^12/l)</td>
<td>359 (132–1,634)</td>
</tr>
<tr>
<td>Polymorphonuclear cell (×10^12/l)</td>
<td>255 (69–1,021)</td>
</tr>
<tr>
<td>Mononuclear cell (×10^12/l)</td>
<td>106 (31–294)</td>
</tr>
</tbody>
</table>

Values are presented as number (%), mean±standard deviation (range), or median (interquartile range).
CNS: central nervous system; TBI: traumatic brain injury; CSF: cerebrospinal fluid.
Only two patients had measurable CSF lactate (4.15 and 4.30 mmol/L). Sixty patients (85.7%) presented with hypoalbuminemia (<3.4 g/dL).

A microbiological agent was identified in 21 patients (30%) (Table 3). Only nine patients (12.9%) had a positive CSF culture. Fifty patients (71.4%) were treated with antibiotics in the week before diagnosis; of the patients with sterile CSF cultures, 38 (67%) were treated with antibiotics during the week before diagnosis. Bacteria were identified in 19 cases (27.1%), with a predominance of Gram-negative (n=13, 18.6%) over Gram-positive (n=8, 11.4%) bacteria. Three infections were polymicrobial, and there was one mixed bacterial and fungal infection. Two infections were strictly fungal, one by *Candida albicans* and another by *Candida parapsilosis*. Two strains of *Staphylococcus epidermidis* were multi-drug resistant, and one strain of *Escherichia coli* produced extended-spectrum beta-lactamases.

Patients were treated with antimicrobial therapy for an average of 15±9 days (range, 1–52); when patients with fewer than 10 days of therapy were excluded (minimum accepted treatment duration), mean antimicrobial therapy was 18±8 days (range, 10–52) (Table 4). One patient was treated with intraventricular therapy after having no response to intravenous therapy. Only two patients had their device removed because of infection. Twenty-one patients (30%) required neurosurgery after diagnosis; however, only five were directly related to CNS infection (drainage of empyema or abscess, subdural space lavage, surgical wound debridement, or closure of CSF fistula) and two underwent decompressive craniectomy. Sixty-four patients (91.4%) required endotracheal intubation, but only 17 (24.3%) required it after developing CNS infection signs or symptoms.

Patient outcomes are presented in Table 5. Median hospital stay length was 38 days (IQR, 30–46; range, 7–408), and mean ICU stay was 18±12 days (range, 1–53). Of the patients who developed nosocomial meningitis during the ICU stay, diagnosis was established, on average, 8±6 days after ICU admission (range, 0–43). Only five patients (7.1%) required readmission to the ICU, of whom two were due to CNS infection; mean time to ICU readmission after discharge was 9±5 days (range, 2–13).

Thirty-three patients (47.1%) developed complications; 17

---

**Table 3. Microbiological results**

<table>
<thead>
<tr>
<th>Microbiologic result</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive culture</td>
<td>21 (30.0)</td>
</tr>
<tr>
<td>CSF</td>
<td>9 (12.9)</td>
</tr>
<tr>
<td>Blood</td>
<td>12 (17.1)</td>
</tr>
<tr>
<td>Other (CNS biopsy, exudate)</td>
<td>5 (7.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infectious agent</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Candida albicans</em></td>
<td>2 (2.9)</td>
</tr>
<tr>
<td><em>Candida parapsilosis</em></td>
<td>1 (1.4)</td>
</tr>
<tr>
<td><em>Citrobacter braakii</em></td>
<td>1 (1.4)</td>
</tr>
<tr>
<td><em>Corynebacterium species</em></td>
<td>1 (1.4)</td>
</tr>
<tr>
<td><em>Enterobacter aerogenes</em></td>
<td>1 (1.4)</td>
</tr>
<tr>
<td><em>Enterobacter cloacae</em></td>
<td>2 (2.9)</td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em></td>
<td>1 (1.4)</td>
</tr>
<tr>
<td><em>Enterococcus faecium</em></td>
<td>1 (1.4)</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>4 (5.7)</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>3 (4.3)</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>1 (1.4)</td>
</tr>
<tr>
<td><em>Serratia marcescens</em></td>
<td>2 (2.9)</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>2 (2.9)</td>
</tr>
<tr>
<td><em>Staphylococcus epidermidis</em></td>
<td>3 (4.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Etiology</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strictly bacterial</td>
<td>18 (25.7)</td>
</tr>
<tr>
<td>Gram-negative bacterial infection</td>
<td>11 (15.7)</td>
</tr>
<tr>
<td>Gram-positive bacterial infection</td>
<td>6 (8.6)</td>
</tr>
<tr>
<td>Both (Gram-positive and Gram-negative)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Fungal</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Mixed fungal and bacterial</td>
<td>1 (1.4)</td>
</tr>
</tbody>
</table>

**Table 4. Treatment**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical antimicrobial therapy</td>
<td></td>
</tr>
<tr>
<td>Ceftazidime plus vancomycin</td>
<td>42 (60)</td>
</tr>
<tr>
<td>Meropenem plus vancomycin</td>
<td>22 (31.4)</td>
</tr>
<tr>
<td>Route of therapy</td>
<td></td>
</tr>
<tr>
<td>Intravenous only</td>
<td>69 (98.6)</td>
</tr>
<tr>
<td>Intravenous and intraventricular</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Duration of antibiotic therapy (day)*</td>
<td>18.0±8.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other therapeutic measure</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticoid</td>
<td>13 (19.4)</td>
</tr>
<tr>
<td>Intracranial hypertension management</td>
<td></td>
</tr>
<tr>
<td>Antiedematous therapy</td>
<td>8 (11.4)</td>
</tr>
<tr>
<td>Barbiturate coma therapy</td>
<td>2 (2.8)</td>
</tr>
<tr>
<td>CSF shunt</td>
<td>11 (15.7)</td>
</tr>
<tr>
<td>Cranectomy</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Neurosurgery for infection control</td>
<td>4 (5.7)</td>
</tr>
<tr>
<td>Removal of CNS device</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Closure of CSF fistula</td>
<td>1 (1.4)</td>
</tr>
</tbody>
</table>

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

CSF: cerebrospinal fluid; CNS: central nervous system.

*Exclusion of patients treated with <10 days of antibiotics.*
Valdoleiros SR, et al. Nosocomial meningitis in intensive care

Table 5. Outcomes

<table>
<thead>
<tr>
<th>Complication</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>33 (47.1)</td>
</tr>
<tr>
<td>Organ failure</td>
<td></td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>37 (52.9)</td>
</tr>
<tr>
<td>Shock with vasopressor support</td>
<td>21 (30)</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>11 (15.7)</td>
</tr>
<tr>
<td>Hematologic dysfunction</td>
<td>12 (17.1)</td>
</tr>
<tr>
<td>Hepatic dysfunction</td>
<td>8 (11.4)</td>
</tr>
<tr>
<td>Intracranial hypertension</td>
<td>14 (20)</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>6 (8.6)</td>
</tr>
<tr>
<td>Brain abscess</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Cerebral venous sinus thrombosis</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Cerebral vasculitis</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Amaurosis</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Glasgow coma score at discharge</td>
<td></td>
</tr>
<tr>
<td>3–8 Points</td>
<td>4 (5.7)</td>
</tr>
<tr>
<td>9–13 Points</td>
<td>13 (18.6)</td>
</tr>
<tr>
<td>14–15 Points</td>
<td>35 (50.0)</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
</tr>
<tr>
<td>Death during hospitalization</td>
<td>15 (21.4)</td>
</tr>
<tr>
<td>Death during ICU</td>
<td>10 (14.3)</td>
</tr>
<tr>
<td>Death within 30 days after admission</td>
<td>15 (21.4)</td>
</tr>
<tr>
<td>Death during and after hospitalization</td>
<td>26 (37.1)</td>
</tr>
<tr>
<td>Length of stay</td>
<td></td>
</tr>
<tr>
<td>Hospital length of stay in days</td>
<td>38 (30–46)</td>
</tr>
<tr>
<td>ICU length of stay in days</td>
<td>18±12 (1–53)</td>
</tr>
<tr>
<td>Readmission</td>
<td></td>
</tr>
<tr>
<td>Readmission</td>
<td>5 (7.1)</td>
</tr>
<tr>
<td>Readmission related to CNS infection</td>
<td>2 (2.9)</td>
</tr>
</tbody>
</table>

Values are presented as number (%), median (interquartile range), or mean±standard deviation (range).

ICU: intensive care unit; CNS: central nervous system.

patients (24.2%) were discharged with GCS <14. Twenty-six patients died (mortality rate, 37.1%): 15 during hospital admission (10 during ICU admission) and within the first 30 days after CNS infection diagnosis (in-hospital and 30-day mortality rate, 21.4%), and the remaining 11 patients died after hospital discharge.

Comparative Analysis

Comparative analysis results are shown in Table 6. Regarding complications, we found no association with age, immunocompromised status, clinical features, or laboratory findings. Use of meropenem over ceftazidime, both in association with vancomycin, and therapy with steroids were associated with complications (odds ratio [OR], 3.15; 95% confidence interval [CI], 1.08–9.22; P=0.033 and OR, 3.54; 95% CI, 0.97–12.96; P=0.048, respectively). Antiedematous therapy was only used for patients with complications.

The presence of complications, GCS <8 at diagnosis, and antiedematous therapy were not associated with non-alert state at discharge. The two patients who presented with focal deficits at diagnosis and survived were discharged in a non-alert state (P=0.08). Male patients were more likely to be discharged in a non-alert state (OR, 7.60; 95% CI, 0.89–64.62; P=0.04).

Age had no significant impact on patient outcomes, but subgroup analysis of elderly patients (≥65 years old) revealed higher hospital mortality and 30-day mortality (OR, 8.89; 95% CI, 2.42–32.68; P=0.001). Partially dependent patients had higher hospital and 30-day mortality (OR, 9.64; 95% CI, 1.57–59.32; P=0.017). An immunocompromised state was not associated with higher mortality (OR, 1.03; 95% CI, 0.31–3.46; P=1.000). Patients who developed complications had higher hospital and 30-day mortality without statistical significance on univariate analysis (OR, 2.78; 95% CI, 0.83–9.24; P=0.087).

In multivariate analysis (Table 7), the associations of complications with hospital and 30-day mortalities were statistically significant (OR, 5.04; 95% CI, 1.01–25.19; P=0.049). Multivariate analysis of the relationships of age ≥65 years with hospital and 30-day mortality also presented statistical significance (OR, 10.08; 95% CI, 2.03–50.03; P=0.005).

DISCUSSION

Accurate estimates of nosocomial meningitis incidence are hampered by variations in diagnosis, infection definition, institutional infection control, and device manufacturers [1]. Reported incidences vary widely, with overall incidence ranging from <1%–7%, and with postoperative meningitis developing in 0.34%–25% of cases [3,16,17]. We observed an overall incidence within this range, of 0.75%, in critical care patients. To the best of our knowledge, this is the first study of exclusively nosocomial meningitis in a general ICU population that includes both postoperative and non-postoperative patients; thus, we cannot directly compare this incidence with those of other studies.

Evidence of association between demographic characteristics and outcomes in nosocomial meningitis is limited. While Dizbay et al. [18] found higher mortality in younger patients, Srihawan et al. [19] reported that age ≥45 years was associated with higher risk of adverse clinical outcomes, and Lu et al. [20]
Valdoleiros SR, et al.  
Nosocomial meningitis in intensive care

Immunocompromised state, immunosuppressive therapy, diabetes, and alcohol abuse are known risk factors for infection. In ICU patients, major risk factors for nosocomial infections include diabetes mellitus and steroid use [21]. Frontera et al. [10] found a significant association between diabetes and nosocomial meningitis. In our cohort, 12.9% of patients were diabetic, which is consistent with previous reports of 11% [22]. Similarly to Srihawan et al. [19], we did not find an association between immunocompromised state and outcome.

Immunocompromised state, immunosuppressive therapy, diabetes, and alcohol abuse are known risk factors for infection. In ICU patients, major risk factors for nosocomial infections include diabetes mellitus and steroid use [21]. Frontera et al. [10] found a significant association between diabetes and nosocomial meningitis. In our cohort, 12.9% of patients were diabetic, which is consistent with previous reports of 11% [22]. Similarly to Srihawan et al. [19], we did not find an association between immunocompromised state and outcome.

reported higher mortality rate in patients ≥60 years, although only 30% of episodes were due to nosocomial meningitis. In our cohort, patients ≥65 years had significantly higher mortality risk. No significant difference was found regarding complications and non-alert state at discharge between the elderly and non-elderly patients.

Immunocompromised state, immunosuppressive therapy, diabetes, and alcohol abuse are known risk factors for infection. In ICU patients, major risk factors for nosocomial infections include diabetes mellitus and steroid use [21]. Frontera et al. [10] found a significant association between diabetes and nosocomial meningitis. In our cohort, 12.9% of patients were diabetic, which is consistent with previous reports of 11% [22]. Similarly to Srihawan et al. [19], we did not find an association between immunocompromised state and outcome.

The associations between neuroinvasive procedures, head trauma, or subarachnoid hemorrhage and nosocomial meningitis are well established. Several previous studies have

Table 6. Univariate analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Any complication OR (95% CI) P-value</th>
<th>Non-alert at discharge OR (95% CI) P-value</th>
<th>30-Day mortality and hospital mortality OR (95% CI) P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics and underlying disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥65 yr</td>
<td>0.71 (0.26–1.93) 0.51</td>
<td>1.30 (0.28–5.73) 0.71</td>
<td>8.89 (2.42–32.68) 0.001</td>
</tr>
<tr>
<td>Male</td>
<td>1.06 (0.40–2.82) 0.90</td>
<td>7.60 (0.89–64.62) 0.04</td>
<td>0.86 (0.27–2.76) 1</td>
</tr>
<tr>
<td>Previous partially dependent</td>
<td>0.53 (0.09–3.12) 0.68</td>
<td>0.80 (0.69–0.91) 1</td>
<td>9.64 (1.57–59.32) 0.02</td>
</tr>
<tr>
<td>Immunocompromised</td>
<td>0.80 (0.29–2.19) 0.67</td>
<td>1.98 (0.51–7.68) 0.47</td>
<td>1.03 (0.31–3.46) 1</td>
</tr>
<tr>
<td>Clinical feature</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever at diagnosis</td>
<td>0.16 (0.01–1.1) 0.06</td>
<td>1.28 (1.11–1.48) 0.57</td>
<td>0.65 (0.11–3.74) 0.64</td>
</tr>
<tr>
<td>GCS at diagnosis &lt;8 points</td>
<td>0.68 (0.23–2.00) 0.48</td>
<td>4.09 (0.83–20.14) 0.71</td>
<td>0.94 (0.27–3.22) 1</td>
</tr>
<tr>
<td>New focal neurological deficit at diagnosis</td>
<td>5.67 (0.56–57.23) 0.16</td>
<td>- 0.08</td>
<td>3.94 (0.56–28.11) 0.3</td>
</tr>
<tr>
<td>Complication (any)</td>
<td>NA NA 0.45 (0.11–1.92) 0.33</td>
<td>2.78 (0.83–9.24) 0.09</td>
<td></td>
</tr>
<tr>
<td>Hospital stay (mean)</td>
<td>2 (~37 to 13) 0.34</td>
<td>35 (~94 to 61) 0.65</td>
<td>30.4 (12.70–48.05) 0.05</td>
</tr>
<tr>
<td>Laboratory findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-reactive protein ≥100 mg/L</td>
<td>1.29 (0.50–3.31) 0.60</td>
<td>1.00 (0.26–3.77) 1</td>
<td>0.95 (0.30–2.99) 0.93</td>
</tr>
<tr>
<td>CSF white cell ≥100 per μl</td>
<td>1.10 (0.33–3.61) 0.88</td>
<td>3.12 (0.36–27.50) 0.42</td>
<td>0.79 (0.13–4.10) 0.37</td>
</tr>
<tr>
<td>CSF glucose level &lt;0.30 g/L</td>
<td>0.99 (0.24–4.09) 1</td>
<td>3.56 (0.66–19.11) 0.15</td>
<td>1.31 (0.24–7.29) 0.67</td>
</tr>
<tr>
<td>CSF protein level ≥1 g/L</td>
<td>1.52 (0.55–4.17) 0.42</td>
<td>0.51 (0.13–1.96) 0.49</td>
<td>1.42 (0.38–5.31) 0.75</td>
</tr>
<tr>
<td>Concomitant bacteremia</td>
<td>1.15 (0.33–3.98) 0.83</td>
<td>0.63 (0.07–5.88) 1</td>
<td>3.43 (0.90–13.02) 0.11</td>
</tr>
<tr>
<td>Negative CSF culture</td>
<td>0.56 (0.20–1.58) 0.27</td>
<td>0.78 (0.18–3.52) 0.71</td>
<td>0.27 (0.08–0.89) 0.05</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meropenem plus vancomycin</td>
<td>3.15 (1.08–9.22) 0.03</td>
<td>0.96 (0.21–4.30) 1</td>
<td>2.25 (0.63–8.06) 0.31</td>
</tr>
<tr>
<td>Antibiotic treatment &gt;14 days</td>
<td>2.84 (0.91–8.86) 0.07</td>
<td>1.48 (0.29–7.54) 0.70</td>
<td>1.05 (0.19–5.74) 1</td>
</tr>
<tr>
<td>Steroid therapy</td>
<td>3.54 (0.97–12.96) 0.05</td>
<td>4.34 (0.93–20.30) 0.07</td>
<td>2.22 (0.56–8.82) 0.26</td>
</tr>
<tr>
<td>Antiedematous therapy (including barbiturates)</td>
<td>- 0.001</td>
<td>1.41 (0.24–8.16) 0.65</td>
<td>- 0.19</td>
</tr>
<tr>
<td>CSF shunt</td>
<td>1.42 (0.39–5.18) 0.59</td>
<td>0.45 (0.05–4.04) 0.67</td>
<td>0.79 (0.15–4.10) 1</td>
</tr>
<tr>
<td>Neurology consult</td>
<td>0.92 (0.34–2.48) 0.87</td>
<td>5.25 (1.29–21.40) 0.03</td>
<td>1.37 (0.42–4.44) 0.60</td>
</tr>
<tr>
<td>Neurosurgery consult</td>
<td>1.69 (0.45–6.40) 0.44</td>
<td>1.58 (0.17–14.66) 1</td>
<td>0.40 (0.10–1.61) 0.23</td>
</tr>
</tbody>
</table>

OR: odds ratio; CI: confidence interval; GCS: Glasgow coma scale; NA: non-applicable; CSF: cerebrospinal fluid.

Table 7. Multivariate analysis for 30-day mortality and hospital mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI) P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥65 yr</td>
<td>10.08 (2.03–50.03) 0.01</td>
</tr>
<tr>
<td>Male</td>
<td>1.15 (0.25–5.32) 0.86</td>
</tr>
<tr>
<td>Previous partially dependent</td>
<td>4.45 (0.42–46.70) 0.21</td>
</tr>
<tr>
<td>Complications (any)</td>
<td>5.04 (1.01–25.19) 0.05</td>
</tr>
<tr>
<td>Negative CSF culture</td>
<td>0.53 (0.07–1.30) 0.11</td>
</tr>
</tbody>
</table>

OR: odds ratio; CI: confidence interval; CSF: cerebrospinal fluid.
analyzed cohorts of nosocomial meningitis after CNS surgical intervention [17,22-25]. In contrast, nosocomial meningitis as a complication of bacteremia is rare [4]. We estimated a 7.1% incidence of nosocomial meningitis due to bacteremia, which is higher than expected. Nevertheless, all remaining patients had CNS-related risk factors for nosocomial meningitis.

Fever and altered mental status were the most frequent clinical signs, consistent with current evidence [4]. However, these characteristics are nonspecific and often unhelpful for differential diagnosis of possible foci of infection, especially in critical patients. In a prospective study in a neurologic ICU, fever occurred in nearly 25% of patients, of which more than half (52%) were noninfectious [26]. In severely brain-injured patients, this proportion is even higher, reaching 78% during the first week of hospitalization [27]. Altered mental status can have a multitude of possible causes, including drugs, sepsis, electrolyte disturbances, hypercarbia, and hypoxemia, none of which are rare in an ICU. Moreover, the predisposing condition for meningitis itself (head injury, intracranial bleeding, subarachnoid hemorrhage, or tumor) can cause decreased consciousness. Nonetheless, fever and/or deteriorating mental status in the absence of another clear source of infection and in the context of recent head trauma or neurosurgery should always raise suspicion for CNS infection and prompt CSF analysis.

Shi et al. [28] concluded that a GCS score <9 was related to substandard outcomes, and Erdem et al. [29] described GCS score <10 as an independent risk factor for mortality, while Kim et al. [22] did not find any association between a semicomatose or comatose mental state and mortality. We did not observe any association between GCS score at diagnosis and mortality.

Abnormalities in CSF cell count, glucose, and protein might be unreliable indicators for infection presence in patients with health-care associated ventriculitis and meningitis [11]. For instance, surgery, trauma, and intracranial hemorrhage can all induce CSF abnormalities, and aseptic inflammation can result from tissue response to injury or stimulation by non-infectious agents [13]. CSF pleocytosis, including polymorphonuclear pleocytosis, is particularly unreliable, as it can be reactive to prior neurosurgical interventions or devices [12]. Two previous studies have shown that a low CSF glucose level correlated with higher mortality [20,29], but two other studies did not show such an association [19,22]. In our cohort, we did not find an association between CSF glucose level and mortality.

It is estimated that at least 11%–30% of nosocomial meningitis is culture negative [1]. We observed an elevated rate of culture-negative CNS infection (70%), which we postulate might be due to high selective pressure by antibiotics in ICU patients or over-valorization of clinical and analytical CSF features. According to CDC criteria, fever and CSF pleocytosis with elevated protein and/or decreased glucose and appropriate antimicrobial therapy are the criteria for diagnosis of nosocomial meningitis. Despite fulfilling these criteria, we suspect that meningeal reactions to TBI or cerebral hemorrhage, for example, are over-diagnosed as meningitis.

Cutaneous Gram-positive bacteria, such as coagulase-negative Staphylococci, Staphylococcus aureus, and Cutibacterium acnes, are the main etiological agents of nosocomial meningitis [1]. However, the proportion of Gram-negative infections is increasing [1,3], with a reported prevalence as high as 52% [2]. Accordingly, we observed a higher incidence of Gram-negative meningitis (15.7% vs. 8.6%), but the number of culture-positive cases was too low to draw conclusions. When comparing meningitis due to Gram-negative bacteria to meningitis due to Gram-positive bacteria, some studies found that the former was associated with higher mortality [2,18]. In contrast, we did not observe a significant difference in mortality among culture-positive and culture-negative meningitis.

As expected, therapy with steroids was not associated with lower mortality. Although attenuation of subarachnoid space inflammatory response by steroid use might be effective in decreasing many of the pathophysiologic consequences of bacterial meningitis (cerebral edema, increased intracranial pressure, altered cerebral blood flow, cerebral vasculitis, and neuronal injury), these patients generally require antimicrobial therapy with vancomycin (at least during the empiric phase of antimicrobial therapy), and the diminished inflammatory response induced by dexamethasone might reduce CSF vancomycin penetration [30]. Steroid use was associated with a higher complication rate, possibly because steroids are mostly used in this setting.

The mortality rate of nosocomial meningitis ranges from 8%–50% [2,18-20,23,28,29,31,32]. Most studies are of patients with post-neurosurgical or post-traumatic meningitis and do not distinguish between critically and non-critically ill patients, which can be a confusing factor when comparing it to our cohort. Two studies reported mortality rates of 39.7% [2] and 50% [33] in post-neurosurgical critically ill patients with nosocomial meningitis. The mortality rate of our cohort, 37.1%, was similar to that of previous studies.
This study has some limitations. First, it is a retrospective single-center study, with only 70 patients. Second, we included all patients that fulfilled CDC criteria for nosocomial meningitis, regardless of negative CSF cultures or absence of CSF analysis, which might have resulted in an over-estimation incidence. The low pathogen isolation rate also hindered analysis of etiological agents. Multi-center prospective studies with larger populations are needed to improve knowledge and practices on diagnosis, therapy, and outcomes of nosocomial meningitis.

In this study, nosocomial meningitis in critical care had a low incidence rate (0.75%) but a high mortality rate (37.1%) and a significant complication rate (47.1%). Advanced age (≥65 years old) and complications were associated with higher hospital mortality. No clinically relevant factor was predictive of complication development.

Fever and altered mental status were the most consistent clinical signs; however, in critical care, these can be explained by a multitude of other causes. Additionally, this population is frequently prescribed broad-spectrum antibiotics, altering CSF pleocytosis, biochemistry parameters, and cultures. Defining meningitis by the CDC criteria in this population might be encouraging over-diagnosis and over-treatment of this condition. Conversely, an appropriate balance between THE risk of not treating a true CNS infection and THE risk of unnecessary broad-spectrum antibiotic use might be difficult to achieve.

CONFLICT OF INTEREST

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

ACKNOWLEDGMENTS

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AUTHOR CONTRIBUTIONS

Conceptualization: SRV, CT, LSF, CG, CT. Data curation: SRV, CT, LSF, DM. Formal analysis: SRV, CT, LSF, DM, CG. Methodology: SRV, CT, LSF, DM. Project administration: SRV, CT. Validation: SRV, CT, CG. Visualization: SRV, CT. Writing—original draft: SRV, CT, LSF, DM. Writing—review & editing: SRV, CT, LSF, CG, CT.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4266/acc.2021.01151.

REFERENCES


Comparison of high-flow nasal oxygen therapy and noninvasive ventilation in COVID-19 patients: a systematic review and meta-analysis

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Background: Acute respiratory failure (ARF) is a major adverse event commonly encountered in severe coronavirus disease 2019 (COVID-19). Although noninvasive mechanical ventilation (NIV) has long been used in the management of ARF, it has several adverse events which may cause patient discomfort and lead to treatment complication. Recently, high-flow nasal cannula (HFNC) has the potential to be an alternative for NIV in adults with ARF, including COVID-19 patients. The objective was to investigate the efficacy of HFNC compared to NIV in COVID-19 patients.

Methods: This meta-analysis was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria. Literature search was carried out in electronic databases for relevant articles published prior to June 2021. The protocol used in this study has been registered in International Prospective Register of Systematic Reviews (CRD42020225186).

Results: Although the success rate of NIV is higher compared to HFNC (odds ratio [OR], 0.39; 95% confidence interval [CI], 0.16–0.97; P=0.04), this study showed that the mortality in the NIV group is also significantly higher compared to HFNC group (OR, 0.49; 95% CI, 0.39–0.63; P<0.001). Moreover, this study also demonstrated that there was no significant difference in intubation rates between the two groups (OR, 1.35; 95% CI, 0.86–2.11; P=0.19).

Conclusions: Patients treated with HFNC showed better outcomes compared to NIV for ARF due to COVID-19. Therefore, HFNC should be considered prior to NIV in COVID-19–associated ARF. However, further studies with larger sample sizes are still needed to better elucidate the benefit of HFNC in COVID-19 patients.

Key Words: COVID-19; high-flow nasal cannula; meta-analysis; noninvasive ventilation; systematic review

INTRODUCTION

As the coronavirus disease 2019 (COVID-19) pandemic continues to spread globally, there are already more than 218 million confirmed cases and 4.5 million deaths reported to the World Health Organization in September 2021 [1]. In severe and critical cases of COVID-19, acute respiratory distress syndrome (ARDS) remains one of the most common unwanted
events encountered. ARDS develops in 42% of COVID-19 patients and 61%–81% of those with ARDS requiring intensive care, including advance oxygen therapy [2,3].

Avoiding unnecessary use of invasive ventilation and endotracheal intubation persist a main objective in the management of acute respiratory failure (ARF) as these procedures are associated with severe adverse events and poor outcomes [4]. Therefore, a noninvasive oxygenation strategy has been developed to support oxygenation and tackle the negative outcomes which are often found in the invasive strategy [5]. Noninvasive mechanical ventilation (NIV) is one of the alternative respiratory support strategies to invasive mechanical ventilation in ARF. However, the use of NIV has several potential adverse events, such as sputum retention, difficulty in synchronizing breathing and skin damage over the bridge of the nose which may cause discomfort and lead to the discontinuation of NIV to some extent [6]. In recent years, high-flow nasal cannula (HFNC), a newly introduced noninvasive oxygenation device, is also deemed to have the potential to be an alternative for NIV in adults with ARF. HFNC was found to be non-inferior to NIV in reducing the need for invasive ventilation among adults with ARF [7]. Furthermore, a randomized control study also reported that the intubation rate and mortality rate were lower with HFNC than with NIV [8].

In COVID-19 setting, HFNC has been recommended by The Asian Critical Care Clinical Trials Group as an alternative to NIV in COVID-19 patient with ARF [9]. Despite the weak recommendation, The Surviving Sepsis Campaign COVID-19 subcommittee also recommended HFNC to be the first line oxygen therapy for COVID-19 patients as it has been suggested to be superior to NIV by most of the experts [10]. These recommendations might be made based on recent satisfactory results regarding the use of HFNC in COVID-19 patients. Several studies showed that HFNC was found to be non-inferior to NIV for reducing the intubation rate and mortality rate in COVID-19 patients [11-13]. Moreover, some studies even found that HFNC has the potential to be superior to NIV if used in appropriate patients [8,14]. Hence, it can be postulated that HFNC has the potential to be the preferred treatment prior to NIV in COVID-19–associated ARF. However, there is still limited evidence supporting the advantages of HFNC over NIV in COVID-19 patients. Hence, we design a systematic review of existing studies and perform a meta-analysis to further investigate and measure the efficacy of HFNC compared to NIV in COVID-19 patients.

**KEY MESSAGES**

- High-flow nasal cannula (HFNC) has demonstrated a remarkable ability to match noninvasive mechanical ventilation (NIV) in terms of preventing intubation and even showed more satisfactory results in preventing mortality.
- HFNC should be considered prior to NIV in coronavirus disease 2019 (COVID-19)-associated acute respiratory failure.
- Due to relatively small sample size, further studies with larger sample sizes are still needed to more clearly elucidate the benefit of HFNC in COVID-19 patients.

**MATERIALS AND METHODS**

**Study Registration and Methodology**

This meta-analysis was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria [15]. As this paper did not directly involve human subjects, while only using data from published articles, institutional review board approval was not required. The protocol used in this study has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42020225186).

**Eligibility Criteria**

The following criteria were considered for studies’ eligibility: type of study, population, intervention, comparison, and outcome. All types of clinical studies (randomized or non-randomized clinical trials, cohort, case control and cross-sectional) evaluating the use of HFNC and NIV in the COVID-19 patients were included for this study. Case series, case report, reviews and commentary articles were excluded. The participants of this study are subjects diagnosed with COVID-19 and eligible for the use of advanced oxygen therapy. There were no restrictions on age, races, occupation, economy or social status, religion, country, underlying conditions etc. Studies evaluating HFNC as the oxygen therapy for COVID-19 patients were included for this study. Comparators included COVID-19 patients who were treated with NIV. Outcomes of interest were success rate, intubation rate and mortality rate of HFNC compared to NIV in COVID-19 patients. Success rate is defined as the percentage of successes of HFNC or NIV in providing oxygen to the patient without the need to switch to another oxygen-assisted modality. Intubation rate is defined as the
percentage of intubations performed due to the deterioration of the patient after HFNC or NIV has been installed. Mortality rate is defined as the number of deaths among each group.

Data Sources and Study Selection

Literature search was carried out with multiple electronic databases, such as Medline, ScienceDirect, EBSCO, and ProQuest to identify articles published up to December 2020. The search was performed by five researchers (G, GM, N, FC, BJQ). No time and language restriction were applied. The keywords used were presented in Supplementary Table 1.

After removing duplicates, five reviewers independently screened the titles and abstracts according to the eligibility criteria described above. Thereafter, potentially eligible full-text articles were thoroughly checked by four independent reviewers before including them into the analysis. Reasons for excluding studies were documented. Any emerging discrepancies would be resolved by consensus among the review team. A PRISMA flowchart describing the study selection process was provided. The planned procedure was illustrated in Figure 1.

Data Extraction

At least two reviewers independently extracted the data from eligible articles identified during the screening process. In case of disagreements occurred, it would be resolved through discussion until a consensus was achieved. The following data were extracted from the studies: (1) first author and publication year; (2) region; (3) study design; (4) sample size; (5) sample characteristics (age, sex, pre-existing conditions); (6) PaO2/FiO2; (7) duration of HFNC; (8) duration of NIV; and (9) quality assessment.

Quality Assessment and Reliability of Data

Version 2 of Cochrane Risk of Bias (ROB-2) tool was used to assess the quality of randomized controlled trial [16]. Meanwhile, Newcastle-Ottawa scale (NOS) was used to evaluate the quality of observational studies [17]. Five researchers (G, GM, N, FC, BJQ) independently evaluate the quality of each study with any discrepancies resolved through discussion.

Trial sequential analysis (TSA) was performed to determine the required sample size and confirm whether the result of meta-analysis was conclusive. TSA generated thresholds for

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of literature search and selection process.
declaring significance of the result to avoid the overestimation of intervention effects and prevent spurious results. The findings were represented by the cumulative Z-curves. When the cumulative Z-curves surpassed the futility boundary, the level of evidence was adequate and further trials will be judged as futile. The level of evidence was judged as adequate and conclusive, if the Z-curves surpassed the conventional and trial sequential significance boundaries. On the contrary, when Z-curves did not cross any boundaries or only surpassed the conventional boundary, the level of evidence was inadequate and more trials were required to clarify the conclusion. A two-sided trial sequential monitoring boundary type was used in our TSA. The required information size was calculated with $\alpha=0.05$. TSA was performed using TSA version 0.9.5.10 beta [18].

### Data Synthesis and Statistical Analysis

Odds ratio (OR) with a confidence interval (CI) of 95% was used to determine the efficacy of HFNC compared to NIV in COVID-19 patients. OR was considered significant if the value was not equal to 1 with $P<0.05$. Random effects model was used for the analysis and the combined effect size was plotted using a forest plot. Heterogeneity of included studies are assessed using Cochrane’s Q Test (chi-square) of homogeneity and Higgins $I^2$ statistics. Subgroup analysis would be conducted to find the possible cause of heterogeneity. Funnel plot was used to assess publication bias visually. Asymmetric funnel plot indicated the possibility of publication bias. This would be confirmed through Begg and Mazumdar rank correlation test and Egger’s test of the intercept to determine the presence of publication bias statistically. If publication bias was observed, Duval and Tweedie’s trim and fill method would be used to correct the bias. Furthermore, sensitivity analysis was performed in order to confirm the robustness of this meta-analysis. All statistical tests were done using RevMan 5.3 (Cochrane Collaboration, London, UK) [19].

### Confidence in Cumulative Evidence

Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) was used to determine the confidence in cumulative evidence. Judgement was made considering the presence of study limitations, consistency, directness, imprecision, and/or reporting bias. Overall certainty of evidence was shown as high, moderate, low, or very low quality.

### RESULTS

#### Search Results

Initial search from the electronic database yielded 4,206 studies, of which 1,327 were duplicates and therefore excluded. The remaining 2,879 articles were screened through titles and abstracts. Moreover, a total of 2,781 studies were excluded as it was found to be irrelevant to the topic of our study and 98 studies were further assessed for eligibility. At last, 10 studies were included in our systematic review and meta-analysis. The searching strategy and selection methods of this study were illustrated in Figure 1.

#### Study Characteristics

The majority of included studies are conducted in China (4 studies) [11,14,20,21], followed by Switzerland (2 studies) [22,23], Belgium (1 study) [24], France (1 study) [24], Italy (2 study) [12,25], Austria (1 study) [24], Greece (1 study) [26]. One included study was a randomized clinical trial and the rest of the included studies were categorized as observational study, which were either prospective or retrospective. Six included studies were a multi-center study and the rest were a single-center study. The participants were adults with ages ranging from 36 to 75 years old. All the study participants showed PaO2/FiO2 ratio under 300 mm Hg [27]. Characteristics of included studies were presented in Table 1.

#### Methodological Quality

A randomized controlled trial was evaluated using Cochrane ROB-2 and judged to have low risk of bias. Quality assessment of the observational studies were conducted using NOS. Based on the findings, the overall quality of all included studies was considered as good with a mean score of 8. There were four studies which did not provide adequate information regarding the follow up of the cohort study. However, it did not affect the overall quality of evidence of these studies because the other point of outcomes’ assessments was provided with adequate information [14,21,24,26]. A complete summary of the quality assessment was presented in Table 2 and Supplementary Figure 1.

#### Mortality Rate

A meta-analysis of nine studies which was presented in Figure 2A showed THAT HFNC was associated with a lower mortality rate compared to NIV (OR, 0.49; 95% CI, 0.39–0.63; $P<0.001$; $I^2$, 0%). Moreover, TSA also confirmed this result as the cumula-
Table 1. Characteristics of studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Region</th>
<th>Study type</th>
<th>Sample size</th>
<th>Age (yr)</th>
<th>PaO2/FiO2</th>
<th>HFNC setting</th>
<th>NIV setting</th>
<th>Quality assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>COVID-ICU Group</td>
<td>France, Switzerland, and Belgium</td>
<td>Multi-center, prospective, cohort study</td>
<td>HFNC: 23, NIV: 13</td>
<td>63 (54–71)</td>
<td>Overall sample: 154 mm Hg (106–223), HFNC: ND, NIV: ND</td>
<td>ND</td>
<td>ND</td>
<td>8 (Good)*</td>
</tr>
<tr>
<td>Duan et al. (2021)</td>
<td>China</td>
<td>Multi-center, retrospective, cohort study</td>
<td>HFNC: 23, NIV: 13</td>
<td>HFNC: 65±14, NIV: 50±14</td>
<td>HFNC: &gt;200 mm Hg: 9 (23) 150–200 mm Hg: 10 (44) 100–150 mm Hg: 4 (17) NIV: &gt;200 mm Hg: 3 (23) 150–200 mm Hg: 4 (31) 100–150 mm Hg: 6 (46)</td>
<td>The temperature was set between 31°C and 37°C, the flow was set between 30 and 60 L/min, and the FiO2 was set to maintain the SpO2 more than 93%</td>
<td>NIV delivered by face mask. The initial inspiratory pressure was 8–10 cm H2O. The FiO2 was titrated to main the SpO2 more than 93%.</td>
<td>8 (Good)*</td>
</tr>
<tr>
<td>Franco et al. (2020)</td>
<td>Italy</td>
<td>Multi-center, prospective, observational study</td>
<td>HFNC: 163, NIV: 177</td>
<td>HFNC: 65.7±14.7, NIV: 66.8±13.5</td>
<td>HFNC: 166±65 mm Hg, NIV: 138±66 mm Hg</td>
<td>HFNC was delivered using standard devices (nasal high flow therapy, Fisher and Paykel Healthcare, East Tamaki, New Zealand)</td>
<td>NIV was delivered by single-circuit NIV platforms provided with an oxygen blender and ad hoc filters.</td>
<td>9 (Good)*</td>
</tr>
<tr>
<td>Wendel Garcia et al. (2021)</td>
<td>Switzerland</td>
<td>Prospective, cohort study</td>
<td>HFNC: 10, NIV: 12</td>
<td>63 (53–71)</td>
<td>HFNC: 136 mm Hg (90–194), NIV: ND</td>
<td>ND</td>
<td>ND</td>
<td>8 (Good)*</td>
</tr>
<tr>
<td>Grieco et al. (2021)</td>
<td>Italy</td>
<td>Multi-center, randomized, clinical trial</td>
<td>HFNC: 55, NIV: 54</td>
<td>HFNC: 63 (55–69), NIV: 66 (57–72)</td>
<td>HFNC: 102 mm Hg (80–124), NIV: 105 mm Hg (83–125)</td>
<td>HFNC was delivered using standard devices (nasal high flow therapy, Fisher and Paykel Healthcare) continuously for at least 48 hours. Gas flow was initially set at 60 L/min and eventually decreased in case of intolerance, FiO2 titrated to obtain peripheral SpO2 between 92% and 98%, and humidification chamber was set at 33°C or 34°C according to the patient's comfort</td>
<td>NIV was delivered using helmet interface for 48 hours continuously. The ventilator was set in pressure support mode, with the following settings: initial pressure support between 10 and 12 cm H2O, eventually increased to ensure a peak inspiratory flow of 100 L/min; positive end-expiratory pressure between 10 and 12 cm H2O; and FiO2 titrated to obtain SpO2 between 92% and 98%</td>
<td>Low risk*</td>
</tr>
<tr>
<td>Hu et al. (2020)</td>
<td>China</td>
<td>Retrospective, observational study</td>
<td>HFNC: 12, NIV: 15</td>
<td>HFNC: 61.5 (48–76.8), NIV: 64 (56–74)</td>
<td>Overall sample: 193±50.77 mm Hg, HFNC: ND, NIV: ND</td>
<td>ND</td>
<td>ND</td>
<td>9 (Good)*</td>
</tr>
<tr>
<td>Klein et al. (2020)</td>
<td>Austria</td>
<td>Multi-center, prospective, observational study</td>
<td>HFNC: 15, NIV: 52</td>
<td>≤64 yr: 26 (52), ≥65 yr: 24 (48)</td>
<td>Overall sample: 121 mm Hg (86–171), HFNC: ND, NIV: ND</td>
<td>ND</td>
<td>ND</td>
<td>7 (Good)*</td>
</tr>
<tr>
<td>Routsi et al. (2020)</td>
<td>Greece</td>
<td>Prospective, observational study</td>
<td>HFNC: 17, NIV: 9</td>
<td>HFNC: 65 (56–75)</td>
<td>HFNC: 181 mm Hg (130–376), NIV: ND</td>
<td>The temperature was set at 31°C to 37°C, the flow was set at 30 to 60 L/min, and FiO2 was set to maintain the SpO2 more than 93%</td>
<td>NIV delivered by face mask. The initial inspiratory pressure was 8–10 cm H2O. The FiO2 was titrated to main the SpO2 more than 93%.</td>
<td>7 (Good)*</td>
</tr>
<tr>
<td>Wang et al. (2020)</td>
<td>China</td>
<td>Multi-center, retrospective observational study</td>
<td>HFNC: 17, NIV: 9</td>
<td>HFNC: 65 (56–75)</td>
<td>HFNC: 181 mm Hg (130–376), NIV: ND</td>
<td>The temperature was set at 31°C to 37°C, the flow was set at 30 to 60 L/min, and FiO2 was set to maintain the SpO2 more than 93%</td>
<td>NIV delivered by face mask. The initial inspiratory pressure was 8–10 cm H2O. The FiO2 was titrated to main the SpO2 more than 93%.</td>
<td>7 (Good)*</td>
</tr>
<tr>
<td>Wang et al. (2020)</td>
<td>China</td>
<td>Retrospective, observational study</td>
<td>HFNC: 22, NIV: 65</td>
<td>59.2 (428–73.1)</td>
<td>ND</td>
<td>ND</td>
<td>7 (Good)*</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range), mean±standard deviation, or number (%).
HFNC: high-flow nasal cannula; NIV: noninvasive mechanical ventilation; COVID: coronavirus disease; ICU: intensive care unit; ND: no data.
*Newcastle-Ottawa scale; †Cochrane risk of bias tool.
tive Z-curve surpassed the conventional significance boundary as well as the trial sequential significance boundary (Figure 2B). Moreover, the cumulative Z-curve also surpassed the required meta-analysis sample size with a minimal participant of 1,524. Thus, the result was conclusive and no further trials are required.

In addition, we also further evaluate the mortality rate of HFNC when used as a first-line oxygen therapy for severe-to-critical COVID-19 patients. Four studies demonstrated that the mortality rate in the HFNC group was significantly lower than the NIV group (OR, 0.45; 95% CI, 0.27–0.75; P=0.002; I², 0%) in patient who received HFNC and NIV as their first line oxygen therapy (Figure 3A). TSA also confirmed the result as the cumulative Z-curve surpassed the conventional significance boundary as well as the trial sequential significant boundary which implied that type I and type II error was not avoided. Moreover, the cumulative Z-curve also did not reach the required meta-analysis sample size with a minimal participant of 495. Thus, it could be inferred that the result was still inconclusive and further trials were required.

Success Rate
Three studies demonstrated that NIV had a higher success rate than HFNC. The pooled analysis which was presented in Figure 4A, proposed that the success rate of NIV was significantly higher than the HFNC (OR, 0.39; 95% CI, 0.16–0.97; P=0.04; I², 0%). In addition, TSA was also conducted to further confirm the result. As seen in Figure 4B, the cumulative Z-curve only surpassed the conventional significance boundary and did not surpass the trial sequential significant boundary which implied that type II error was not avoided. Moreover, the cumulative Z-curve also did not reach the required meta-analysis sample size with a minimal participant of 495. Thus, it could be inferred that the result was still inconclusive and further trials were required.

Intubation Rate
In this study, we found that HFNC was non-inferior to NIV in reducing the need for intubation. As seen in Figure 5A, a meta-analysis of four studies demonstrated that the outcome of HFNC similar to NIV with respect to the intubation rate (OR, 1.35; 95% CI, 0.86–2.11; P=0.19; I², 9%). To further confirm the result, TSA was also conducted and showed that the cumulative Z-curve did not cross any boundaries which implies that type I and II error were not avoided. Moreover, the cumulative Z-curve also did not reach the required meta-analysis sample size with a minimal participant of 1,684 (Figure 5B). Therefore, the result was still inconclusive and further trials are required.

Confidence in Cumulative Evidence
Overall studies were judged to have good quality according to

Table 2. Methodological quality (observational studies)

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome</th>
<th>Overall quality assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>COVID-ICU group (2020) [23]</td>
<td>★ ★ ★ ★ ★ ★ ★ ★</td>
<td>★ ★ ★ ★ ★ ★ ★ ★</td>
<td>★ ★ ★ ★ ★ ★ ★ ★</td>
<td>8 (Good)</td>
</tr>
<tr>
<td>Duan et al. (2021) [11]</td>
<td>★ ★ ★ ★ ★ ★ ★ ★</td>
<td>★ ★ ★ ★ ★ ★ ★ ★</td>
<td>★ ★ ★ ★ ★ ★ ★ ★</td>
<td>8 (Good)</td>
</tr>
<tr>
<td>Franco et al. (2020) [12]</td>
<td>★ ★ ★ ★ ★ ★ ★ ★</td>
<td>★ ★ ★ ★ ★ ★ ★ ★</td>
<td>★ ★ ★ ★ ★ ★ ★ ★</td>
<td>9 (Good)</td>
</tr>
<tr>
<td>Wendel Garcia et al. (2021) [28]</td>
<td>★ ★ ★ ★ ★ ★ ★ ★</td>
<td>★ ★ ★ ★ ★ ★ ★ ★</td>
<td>★ ★ ★ ★ ★ ★ ★ ★</td>
<td>8 (Good)</td>
</tr>
<tr>
<td>Hu et al. (2020) [20]</td>
<td>★ ★ ★ ★ ★ ★ ★ ★</td>
<td>★ ★ ★ ★ ★ ★ ★ ★</td>
<td>★ ★ ★ ★ ★ ★ ★ ★</td>
<td>9 (Good)</td>
</tr>
<tr>
<td>Klein et al. (2020) [24]</td>
<td>★ ★ ★ ★ ★ ★ ★ ★</td>
<td>★ ★ ★ ★ ★ ★ ★ ★</td>
<td>★ ★ ★ ★ ★ ★ ★ ★</td>
<td>7 (Good)</td>
</tr>
<tr>
<td>Routsi et al. (2020) [26]</td>
<td>★ ★ ★ ★ ★ ★ ★ ★</td>
<td>★ ★ ★ ★ ★ ★ ★ ★</td>
<td>★ ★ ★ ★ ★ ★ ★ ★</td>
<td>7 (Good)</td>
</tr>
<tr>
<td>Wang K et al. (2020) [13]</td>
<td>★ ★ ★ ★ ★ ★ ★ ★</td>
<td>★ ★ ★ ★ ★ ★ ★ ★</td>
<td>★ ★ ★ ★ ★ ★ ★ ★</td>
<td>7 (Good)</td>
</tr>
<tr>
<td>Wang Z et al. (2020) [21]</td>
<td>★ ★ ★ ★ ★ ★ ★ ★</td>
<td>★ ★ ★ ★ ★ ★ ★ ★</td>
<td>★ ★ ★ ★ ★ ★ ★ ★</td>
<td>7 (Good)</td>
</tr>
</tbody>
</table>

COVID: coronavirus disease; ICU: intensive care unit.

*Thresholds for converting the Newcastle-Ottawa scales to Agency for Healthcare Research and Quality standards (good, fair, and poor). Good quality: 3 or 4 stars in selection domain; and 1 or 2 stars in comparability domain; and 2 or 3 stars in outcome/exposure domain; Fair quality: 2 stars in selection domain; and 1 or 2 stars in comparability domain; and 2 or 3 stars in outcome/exposure domain; Poor quality: 0 or 1 star in selection domain; or 0 stars in comparability domain; or 0 or 1 stars in outcome/exposure domain.
NOS and Cochrane ROB2, hence plausible bias was unlikely to seriously alter the results. In addition, we did not observe any serious inconsistency and indirectness that could affect the whole results. However, we observed imprecision in some of the outcomes. Most individual studies assessing the success rate and intubation rate were found to have a wide CI and inconclusive TSA results. The publication bias could not be assessed in all of the outcomes as the number of included studies did not reach 10. Overall, we had very low-to-moderate quality of evidence in this meta-analysis. GRADE evidence profile was generated as shown in Table 3.

**DISCUSSION**

With 10 studies and 1,766 COVID-19 patients included, this study demonstrated that HFNC was superior to NIV in terms of decreasing mortality, especially when used as the first-line oxygen therapy for COVID-19 patients. These findings were in accordance with the previous studies which showed that therapy using HFNC decrease mortality rate compared to using NIV in adults with ARF [9,14,29]. There are several reasons that may explain this finding, but the most convincing evidence is that NIV has been proven to increase the risk for volutrauma [9,29]. NIV can deliver pressure higher than the
targeted tidal volume which will result in higher transpulmonary driving pressure and inspiratory effort. These conditions will eventually cause patient self-inflicted lung injury which detrimentally affects the patient’s outcome, thereby increasing mortality [30,31]. In contrast, HFNC ensures a more reliable delivery of desired FiO2 than NIV by preventing the entry of room air during patient inspiration [32]. Thus, it will flushed-out CO2 continuously from the upper airway and eliminates the anatomical dead space, further increasing the efficiency of ventilation.

Furthermore, HFNC also provides a small amount of positive end-expiratory pressure (PEEP) which may counterbalance auto-PEEP and reduce the inspiratory effort [33,34]. By combining the washout effect on the upper airway and the generation of a small PEEP, HFNC is able to decrease the work of breathing and improve the ventilation and perfusion matching without increasing tidal volume [34]. Therefore, HFNC may have a lower risk of aggravating lung injury as it prevents excessive lung expansion. Another possible reason is that HFNC has a more superior effect on airway secretion. In patients with pneumonia, management of airway secretion is essential as sputum retention can lead to airway obstruction which can adversely affect the clinical outcome. By delivering humidified gas, HFNC helps optimize mucosal clearance, controlling secretions volume and facilitating cough thereby preventing atelectasis [35]. On the contrary, NIV is reported to be unable to improve sputum clearance [36]. However, it should be noted that the use of HFNC in different cases is not consistently associated with lower mortality. In a recent Cochrane review comparing the efficacy of HFNC with standard oxygen therapy and NIV in adult intensive care patients, HFNC was shown to not exhibit significantly lower mortality and better outcomes.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>HFNC</th>
<th>NIV</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duan 2020</td>
<td>1</td>
<td>23</td>
<td>3.1%</td>
<td>0.55 (0.03, 9.52)</td>
<td>0.43 (0.26, 0.73)</td>
</tr>
<tr>
<td>Franco 2020</td>
<td>26</td>
<td>163</td>
<td>91.7%</td>
<td>1.27 (0.07, 22.72)</td>
<td>0.56 (0.02, 17.92)</td>
</tr>
<tr>
<td>Hu 2020</td>
<td>1</td>
<td>12</td>
<td>3.1%</td>
<td>0.56 (0.02, 17.92)</td>
<td>0.43 (0.26, 0.73)</td>
</tr>
<tr>
<td>Routsi 2020</td>
<td>1</td>
<td>14</td>
<td>2.1%</td>
<td>0.43 (0.26, 0.73)</td>
<td>0.56 (0.02, 17.92)</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>212</strong></td>
<td><strong>207</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.45 (0.27, 0.75)</strong></td>
<td><strong>0.45 (0.27, 0.75)</strong></td>
</tr>
</tbody>
</table>

**Figure 3.** Mortality rate of high-flow nasal cannula (HFNC) compared to noninvasive mechanical ventilation (NIV) if used as the first line therapy only. (A) Forest plot depicting HFNC compared to NIV on mortality rate when used as the first line oxygen therapy. The results demonstrate a difference in mortality rate using a random effects model comparing HFNC vs. NIV. (B) Trial sequential analysis comparing success rate between HFNC and NIV. A 27% control event rate and a 54.8% relative risk reduction with 95% power and a two-sided α=0.05 were assumed. The cumulated Z-curve (blue) surpassed the conventional significance boundary, trial sequential boundary and the required meta-analysis sample size boundary, indicating that the cumulative evidence is conclusive and no further trials are needed. CI: confidence interval.
compared with other modalities [37].

This study also showed that HFNC had a similar outcome to NIV in terms of the need for intubation. On the other hand, this result contradicts another study showing lower intubation rates in the HFNC group compared to the NIV group. However, this finding might be explained by the prolonged use of non-invasive ventilation described in this study which consequently resulted in delayed intubation and led to lower intubation rates due to higher mortality rates without intubation [28]. However, the difference in intubation rates between HFNC and NIV in this study was shown to be inconclusive in the TSA and thus further trials are required.

Despite having several advantages over NIV, our study oddly found that HFNC had a lower success rate than NIV to achieve the desired therapeutic goal. This finding is not surprising as another study has also reported a similar result when comparing HFNC and NIV as the first-line therapy for ARF [30]. However, it should be noted that the primary goal in the management of ARF is to prevent patient deterioration and thereby reduce mortality. Although the success rate of NIV is higher compared to HFNC, the mortality in the NIV group is also significantly higher. Therefore, if faced with a choice, it would be more appropriate to prioritize HFNC over NIV to be the first line oxygen therapy in COVID-19–associated ARF.

The overall quality of evidence was identified as very low-to-moderate. There were inconsistencies for the analysis of success rate and intubation rate. A possible explanation was the small number of subjects used in individual studies or low variability of the population. Due to some inconsistencies, we suggest a weak recommendation for using HFNC as an alternative to NIV in COVID-19 patients.

Strengths of our review include that this is the first meta-analysis that comprehensively compared the efficacy of HFNC and NIV in COVID-19 patients. This study provides early evidence that HFNC may be the preferred modality prior to NIV for COVID-19 patients. However, this study also has sever-
Figure 5. Intubation rate of high-flow nasal cannula (HFNC) compared to noninvasive mechanical ventilation (NIV). (A) Forest plot depicting HFNC compared to NIV on intubation rate. The results demonstrate no difference in intubation rate was noted using a random effects model. (B) Trial sequential analysis comparing success rate between HFNC and NIV. A 26.1% control event rate and a 6.4% relative risk reduction with 95% power and a two-sided $\alpha = 0.05$ were assumed. The trial sequential boundary, futility boundary and the required meta-analysis sample size boundary were not renderable due to too little information used (1.11%) during the analysis. The cumulated Z-curve (blue) did not surpass any boundary, indicating the result was still inconclusive. CI: confidence interval.

Table 3. GRADE evidence profile (HFNC compared to NIV for COVID-19 patients)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of participants (studies)</th>
<th>Risk of bias (NOS, Cochrane ROB2)</th>
<th>Quality assessment</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Not serious Not serious Not serious Serious</td>
<td>NA</td>
<td>Very low</td>
</tr>
<tr>
<td><strong>Success rate</strong></td>
<td>104 (3 cohort studies)</td>
<td>Not serious Not serious Not serious Serious</td>
<td>NA</td>
<td>Very low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>27/61</td>
<td>26/43</td>
<td>0.39 (0.16–0.97)</td>
</tr>
<tr>
<td>Intubation rate</td>
<td>511 (1 RCT, 3 cohort studies)</td>
<td>Not serious Not serious Not serious Serious</td>
<td>NA</td>
<td>Very low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>81/258</td>
<td>68/253</td>
<td>1.35 (0.86–2.11)</td>
</tr>
<tr>
<td>Mortality rate in general</td>
<td>1,740 (1 RCT, 8 cohort studies)</td>
<td>Not serious Not serious Not serious Not serious</td>
<td>NA</td>
<td>Very low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>268/1,111</td>
<td>242/629</td>
<td>0.49 (0.39–0.63)</td>
</tr>
<tr>
<td>Mortality rate if used as first-line therapy</td>
<td>419 (4 cohort studies)</td>
<td>Not serious Not serious Not serious Not serious</td>
<td>NA</td>
<td>Very low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>29/212</td>
<td>56/207</td>
<td>0.45 (0.27–0.75)</td>
</tr>
</tbody>
</table>

GRADE: Grading of Recommendations, Assessment, Development, and Evaluations; HFNC: high-flow nasal cannula; NIV: noninvasive mechanical ventilation; COVID-19: coronavirus disease 2019; NOS: Newcastle-Ottawa scale; OR: odds ratio; CI: confidence interval; NA: not applicable; RCT: randomized controlled trial.

*Most of the individual studies have a wide CI and affected the overall CI to be wide. TSA was inconclusive; **Publication bias could not be determined as the number of studies was less than 10.
al limitations. First, the majority of included studies are observational studies where the characteristics of both groups were not controlled. Second, this study only compared HFNC with NIV in general, thus the comparison results are less specific. Third, this study was unable to provide important information regarding the HFNC/NIV settings and PF ratio in some of the included studies. Lastly, only one randomized clinical trial as the highest position on the evidence pyramid was included in this meta-analysis. These limitations support the need for further larger studies to provide credible results.

HFNC has been shown to be effective as an oxygen delivery modality for ARF. Among severe-to-critical COVID-19 patients, ARF is one of the most common unwanted events encountered and must be treated immediately. In this study, HFNC demonstrated a remarkable ability to significantly decrease the intubation rate and have a lower mortality. By knowing the effectiveness of HFNC in COVID-19 patients, our data suggested that HFNC should be considered prior to NIV in COVID-19-associated ARF. However, further clinical and physiological studies are still needed to more clearly elucidate the benefit of HFNC in COVID-19 patients.

CONFLICT OF INTEREST

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

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AUTHOR CONTRIBUTIONS

Conceptualization: G, BJO. Data curation: all authors. Formal analysis: G, GM, BJO. Methodology: G, GM, N. Project administration: all authors. Visualization: G, FC, N. Writing/original draft: all authors. Writing-review & editing: G, FC, BJO.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4266/acc.2021.01326.

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Clinical characteristics and outcomes of critically ill COVID-19 patients in Sfax, Tunisia

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Background: Africa, like the rest of the world, has been impacted by the coronavirus disease 2019 (COVID-19) pandemic. However, only a few studies covering this subject in Africa have been published.

Methods: We conducted a retrospective study of critically ill adult COVID-19 patients—all of whom had a confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection—admitted to the intensive care unit (ICU) of Habib Bourguiba University Hospital (Sfax, Tunisia).

Results: A total of 96 patients were admitted into our ICU for respiratory distress due to COVID-19 infection. Mean age was 62.4±12.8 years and median age was 64 years. Mean arterial oxygen tension (PaO₂)/fractional inspired oxygen (FiO₂) ratio was 105±60 and ≤300 in all cases but one. Oxygen support was required for all patients (100%) and invasive mechanical ventilation for 38 (40%). Prone positioning was applied in 67 patients (70%). Within the study period, 47 of the 96 patients died (49%). Multivariate analysis showed that the factors associated with poor outcome were the development of acute renal failure (odds ratio [OR], 6.7; 95% confidence interval [CI], 1.75–25.9), the use of mechanical ventilation (OR, 5.8; 95% CI, 1.54–22.0), and serum cholinesterase (SChE) activity lower than 5,000 UI/L (OR, 5.0; 95% CI, 1.34–19).

Conclusions: In this retrospective cohort study of critically ill patients admitted to the ICU in Sfax, Tunisia, for acute respiratory failure following COVID-19 infection, the mortality rate was high. The development of acute renal failure, the use of mechanical ventilation, and SChE activity lower than 5,000 UI/L were associated with a poor outcome.

Key Words: COVID-19; intensive care unit; prognosis; respiratory distress

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the coronavirus responsible for the coronavirus disease 2019 (COVID-19) pandemic that originated in China and spread rapidly worldwide. COVID-19 has affected 219 countries, with more than 118 million infected patients and more than 2.6 million deaths reported [1]. In Africa, more than 4 million cases have been reported, with more than 239,000 cases confirmed in Tunisia [1]. Cough and fever are the most prevalent symptoms, whereas gastrointes-
tinal symptoms are relatively less common [2]. Severe cases of acute COVID-19 infection are generally characterized by acute respiratory distress, and the most frequently reported cause of death is refractory hypoxemia. In fact, it is well established that up to 5% of COVID-19 infected patients develop severe acute respiratory failure requiring intensive care unit (ICU) admission, as well as invasive and/or non-invasive mechanical ventilation (NIV) as supportive care. Moreover, the mortality rate reported worldwide for COVID-19 infected patients requiring ICU admission ranges from 17% to 62% [3].

In Africa, there is little information available about the clinical characteristics and prognosis of COVID-19-infected patients [4-8]. Global mortality rates range from 4% to 5.6% [4-8]. In-hospital mortality is high, in particular for patients with acute respiratory distress requiring ICU admission and mechanical ventilation [4-8]. In fact, the mortality rate reported in severe cases ranges from 50% to 100% [4-8]. However, to the best of our knowledge, apart from some reported cases [9,10], there have been no studies from Tunisia concerning severe cases of patients with COVID-19 requiring ICU admission. We conducted this study to describe the clinical features and outcomes of severely ill patients with COVID-19 infection in Sfax, Tunisia.

**MATERIALS AND METHODS**

This study was approved by the Institutional Review Board of Habib Bourguiba University Hospital (IRB No. 309/2021) and the requirement for written informed consent was waived by the ethics committee. This was a retrospective study of critically ill adult COVID-19 patients—all of whom had a confirmed SARS-CoV-2 infection—admitted between 01 September (the first case) and 04 December 2020 into the ICU of Habib Bourguiba University Hospital. In fact, in Sfax and during the first wave (March-May 2020) of the COVID-19 pandemic, the number of COVID-19 infected patients was very low (less than 60 patients) and all were admitted to the COVID department. During the second wave, severe COVID-19 cases characterized by acute respiratory distress were all hospitalized in the ICU of Habib Bourguiba University Hospital. Our COVID-19 ICU department is a 16-bed, medical-surgical ICU in a teaching hospital of 510 beds that serves as a first-line medical center for an urban population of more than one million inhabitants.

**Case Definition**

The diagnosis of COVID-19 infection was confirmed by reverse transcription polymerase chain reaction testing (kit: genesig real-time PCR CORONAVIRUS COVID-19; CE IVD; Catalogue no. Z-Path-COVID-19-CE). Tests were performed on nasopharyngeal swabs. We used chest computed tomography (CT) scan results in the early detection of COVID-19 pneumonia [11] when findings were classified by radiologists as being compatible with COVID-19. In fact, the presence of peripheral ground glass opacities associated with multilobe and posterior involvement, bilateral distribution, and subsegmental vessel enlargement (>3 mm), is compatible with the diagnosis of COVID-19 pneumonia in this specific pandemic situation. Chest CT scans were scored as having 0%, 25%, 50%, 75%, or 100% involvement [11].

**KEY MESSAGES**

- In this retrospective cohort study of critically ill patients admitted to an intensive care unit in Sfax, Tunisia, for acute respiratory failure following coronavirus disease 2019 (COVID-19) infection, the mortality rate was high (49%).
- The development of acute renal failure, the use of mechanical ventilation, and serum cholinesterase activity lower than 5,000 UI/L were associated with poor outcomes.
In our ICU, the severity of illness was evaluated by the Simplified Acute Physiology Score (SAPS) II [12] and Sequential Organ Failure Assessment (SOFA) score [13]. Overweight and obesity were defined as a body mass index (BMI) ≥25 kg/m² and BMI ≥30 kg/m², respectively [14]. Acute respiratory distress syndrome (ARDS) was defined according to the recently published formal guidelines [15]. According to arterial oxygen tension (PaO₂)/fractional inspired oxygen (FiO₂) ratio, ARDS was classified as mild (200< PaO₂/FiO₂≤300 mm Hg), moderate (100< PaO₂/FiO₂≤200 mm Hg), or severe (PaO₂/FiO₂≤100 mmHg) [15]. FiO₂ for patients able to spontaneously ventilate was calculated using the following formula: FiO₂=(oxygen flow O₂×4)+21%. For all patients, we assessed outcome variables including duration of mechanical ventilation, ICU and hospital length of stay, and ICU mortality.

Management of COVID-19 Patients with Respiratory Distress in Our COVID-19 ICU

In our practice, we used corticosteroids (dexamethasone, 12–24 mg/day) to treat patients with COVID-19 because of the variety of cytokines affected by this steroid (including interleukin [IL]-1, IL-6 and tumor necrosis factor α) [16]. Moreover, acute respiratory distress was treated via high-flow nasal oxygen or facial mask. However, non-invasive and/or invasive mechanical ventilation (IMV) as a supportive treatment was reserved for serious cases with severe hypoxemia. Prone position was also used to treat non-intubated COVID-19 patients and those in hypoxemic acute respiratory failure. For patients who needed IMV, we used a low tidal volume (<6 ml/kg ideal body weight), and airway pressure (plateau pressure <30 cmH₂O) as recommended [17]. For patients with moderate/severe ARDS (PaO₂/FiO₂ ratio<150) requiring IMV, prone positioning was recommended for at least 18 hours per day. Vitamin C (3 g/day), azithromycin, zinc, diuretics (in the absence of shock and/or hypovolemia), and enoxaparin were used in all patients in the absence of contraindications.

Statistical Modeling

All statistical analyses were performed using the IBM SPSS ver. 22 (IBM Corp., Armonk, NY, USA). A P-value less than 0.05 was considered statistically significant. Continuous variables are reported as means (±standard deviation). Categorical variables are reported as proportions and percentages. For univariate analysis of categorical variables, we used the Pearson chi-square or Fisher exact test, as appropriate. The normality of the distribution of continuous variables was examined using the Shapiro-Wilk test. Student t-test was used to assess the significance of differences in normally distributed variables between groups, while the Mann-Whitney U-test was used for non-normally distributed variables. Next, a multivariate logistic regression analysis was performed by using a backward stepwise approach to identify factors predictive of death. Odds ratios and 95% confidence intervals were estimated from the β coefficients obtained. Some variables such as age and severity scores, SAPS II score, SChE activity, and other parameters were used to predict a poor outcome and were analyzed using receiver operating characteristic (ROC) curves. The area under the ROC curve, which was estimated by the method of Hanley and McNeill [18], provides a measure of the predictive accuracy of a test.

RESULTS

Descriptive Characteristics of All Included Patients at Admission

From September 1, 2020, to December 4, 2020, a total of 96 patients were admitted into our ICU for respiratory distress due to a COVID-19 infection. In this study, 77% of patients were male. Mean age was 62.4±12.8 years with a median of 64 years (Table 1), and 41 patients (43%) had a BMI above 30 kg/m². Mean SAPS II on ICU admission was 33±16 (median, 29) and the mean SOFA score on ICU admission was 6±3 (median, 4). Moreover, 78 patients (81%) had one or more comorbidities. The most common pre-existing medical conditions were arterial hypertension in 48 patients (50%) and diabetes mellitus in 44 (46%). The most common symptoms at admission to the hospital were dyspnea in 88 patients (92%), fever (≥38°C) in 63 (66%), and cough in 59 (62%). Extra-pulmonary symptoms, such as headache, were observed in 23 patients (24%), and anosmia/ageusia was observed in 15 patients (15.6%). Mean time elapsed from onset of symptoms to admission was 6.5±4.2 days, and mean time elapsed from symptom onset to ICU admission was 10.7±5.6 days. The most frequent causes of ICU admission were acute respiratory failure (n=89 patients, 92.7%) and coma (5, 5.4%) (Tables 1 and 2). On ICU admission, clinical examination showed that all patients exhibited major
Table 1. Clinical presentation of the study subjects on hospital admission and on the day of ICU admission

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>62.4±12.8</td>
</tr>
<tr>
<td>Obesity (BMI &gt;30 kg/m²)</td>
<td>41 (43)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>44 (46)</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>48 (50)</td>
</tr>
<tr>
<td>Chronic heart disease</td>
<td>8 (8)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>5 (5)</td>
</tr>
<tr>
<td><strong>Symptom on hospital admission</strong></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>88 (92)</td>
</tr>
<tr>
<td>Cough</td>
<td>59 (62)</td>
</tr>
<tr>
<td>Fever</td>
<td>63 (66)</td>
</tr>
<tr>
<td>Headache</td>
<td>23 (24)</td>
</tr>
<tr>
<td>Anosmia/ageusia</td>
<td>15 (16)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13 (14)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>15 (16)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8 (8)</td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation or number (%). The number of patients was 96. ICU: intensive care unit; BMI: body mass index.

Table 2. The clinical presentation the day of ICU admission

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAPS II score</td>
<td>33±16</td>
</tr>
<tr>
<td>SOFA score</td>
<td>6±3</td>
</tr>
<tr>
<td>Cause of ICU admission</td>
<td></td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>89 (93)</td>
</tr>
<tr>
<td>Coma</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Shock</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Clinical finding on ICU admission</td>
<td></td>
</tr>
<tr>
<td>Respiratory rate/min</td>
<td>29±12</td>
</tr>
<tr>
<td>SpO₂ under O₂</td>
<td>87±13</td>
</tr>
<tr>
<td>Signs of respiratory exertion</td>
<td>38 (41)</td>
</tr>
<tr>
<td>Shock</td>
<td>14 (15)</td>
</tr>
<tr>
<td>Body temperature (°C)</td>
<td>37±08</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td>Sedation</td>
<td>48 (50)</td>
</tr>
<tr>
<td>Vasopressor support</td>
<td>36 (38)</td>
</tr>
<tr>
<td>High-flow nasal oxygen</td>
<td>29 (31)</td>
</tr>
<tr>
<td>NIV</td>
<td>48 (50)</td>
</tr>
<tr>
<td>IMV</td>
<td>38 (40)</td>
</tr>
<tr>
<td>Prone positioning</td>
<td>67 (70)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>94 (98)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>71 (74)</td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation or number (%). The number of patients was 96. ICU: intensive care unit; SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment; SpO₂: oxygen saturation measured; NIV: noninvasive ventilation; IMV: invasive mechanical ventilation.

signs of respiratory distress. Mean respiratory rate was 29±12 breaths per minute, mean oxygen saturation measured by pulse oximetry (SpO₂) was 87%±13% under oxygen support via facial mask and 63%±20% in room air. Mean body temperature was at 37°C±0.8°C, and only 12 patients had a body temperature above 38°C. Moreover, 38 patients (41%) showed signs of increased respiratory effort (such as retractions, accessory muscle use, sweating, etc.), and 14 patients (14.6%) developed circulatory failure requiring the infusion of a vasopressor (nor-adrenaline) to maintain a mean arterial pressure of 65 mm Hg or greater. The mean Glasgow coma scale (GCS) score on ICU admission was at 13±3. Ten patients (10.4%) were deeply comatose with a GCS of less than 8. Table 1 summarizes the characteristics of the entire population group on hospital and ICU admission.

Biological and Radiological Findings

Mean pH on ICU admission was 7.40±0.08 with a range of 7.13–7.58. Mean PaO₂/FiO₂ ratio was 105±60, and was ≤ 300 in all cases but one (Table 3). For patients who needed IMV, mean PaO₂/FiO₂ ratio was 69±22, <150 in all patients, and ≤100 (severe ARDS) in 90% of patients. Metabolic acidosis (pH <7.38 and bicarbonate [HCO₃⁻] <22 mmol/L) was observed in 12 patients (14%). Mean blood sugar level on admission was 12.9±6.3 mmol/L (ranging from 3.3 to 32 mmol/L); a high blood sugar level (8 mmol/L) was observed in 78% of cases. Mean plasma protein concentration was 69±8.1 g/L. Mean blood urea was 12.2±9.3 mmol/L, and was >10 mmol/L in 48% of cases. Mean blood creatinine was 107±98 µmol/L, and > 100 µmol/L in 25% of cases. Among the inflammatory parameters recorded at admission for patients with available data, mean leukocyte number was 13,220±6,014 cells/mm³, and >11,000/mm³ in 63% of cases. Mean lymphocyte number was 713±432 cells/mm³, and lymphopenia (≤1,000 cells/mm³) was observed in 79.5% of cases. Mean CRP concentration was 134±152 mg/L, and ≥100 mg/L in 46% of cases. Mean PCT was 1.7±6.1 ng/mL, ranging from 0.1 to 46 ng/mL. SCH E activity was measured for 78 patients on ICU admission (median number of measurements during ICU stay was 2), and mean SCH E activity was 5,857±1,773 UI/L (range, 1,926–10,190 UI/L). Finally, the mean D-dimer value was 1,359±1,430 µg/L. Table 3 summarizes all the biological findings of the entire group.
patient population on ICU admission. At hospital and/or ICU admission, chest CT was performed in 75 patients (78%), and findings were compatible with COVID-19 in 75 of 75 cases (100%). Chest CT scans showed parenchymal opacification with 25% to less than 50% involvement in 14 patients (18.6%), 50% to less than 75% involvement in 31 patients (41%), and 75% or greater involvement in 30 patients (40%). Four patients (4.2%) were diagnosed with pulmonary embolism.

**Treatment and Clinical Outcomes**

During ICU stay, 78 patients (81.0%) received antibiotics, even though only four patients (4.1%) had a confirmed bacterial coinfection. Antibiotics received were azithromycin (n=78, 81%), beta-lactams (n=39, 40%), and levofloxacin (n=25, 26%), and 28 patients (29%) received other antibiotics for nosocomial infections. In addition, corticosteroids were administered to 94 patients (98%). Prophylactic dose anticoagulation for venous thromboembolism was used in 10 patients (10.4%), and therapeutic-dose anticoagulation was used in 86 patients (90%). Vitamin C (3 g/day) was prescribed for all patients, neuromuscular blockers for 38 patients (39.5%), and diuretics for 71 patients (74%). Oxygen support was required for all patients (100%) and was administered via facial mask for 75 (78%), high-flow nasal oxygen for 29 (30.2%), NIV for 48 (50%), and IMV for 38 patients (40%). Among patients requiring IMV, 10 patients were previously treated by high-flow nasal oxygen and 26 previously managed with NIV.

The prone position was applied in 67 patients (70%); it was utilized to treat 29 COVID-19 patients who were not intubated (50%) and 38 patients who were intubated (100%). Extracorporeal membrane oxygenation was used in one patient (1.6%), and 36 (37.5%) patients required vasopressors. Within the study period, 47 of the 96 included patients died (49%). The mean ICU stay was 6.7±5.3 days (median, 5 days). Factors

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Data available for</th>
<th>Mean±SD</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC count (cells/mm³)</td>
<td>88</td>
<td>13,220±6,014.1</td>
<td>12,000 (1,120–31,000)</td>
</tr>
<tr>
<td>Lymphocyte (cells/mm³)</td>
<td>70</td>
<td>713±432.5</td>
<td>600 (100–1,800)</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>88</td>
<td>12.5±2.1</td>
<td>13 (5.5–17.7)</td>
</tr>
<tr>
<td>Platelet count (cells/mm³)</td>
<td>88</td>
<td>303,298±121,920</td>
<td>288,000 (82,000–656,000)</td>
</tr>
<tr>
<td>Blood glucose level (mmol/L)</td>
<td>93</td>
<td>12.9±6.3</td>
<td>11 (3.3–32.1)</td>
</tr>
<tr>
<td>AST (UI/L)</td>
<td>86</td>
<td>41.7±32.7</td>
<td>32 (9.9–204)</td>
</tr>
<tr>
<td>ALT (UI/L)</td>
<td>86</td>
<td>34.1±23.8</td>
<td>24 (7–120.5)</td>
</tr>
<tr>
<td>Total bilirubin (μmol/L)</td>
<td>78</td>
<td>9.4±4.9</td>
<td>8 (4–29)</td>
</tr>
<tr>
<td>Total protein (gL)</td>
<td>66</td>
<td>69.3±8.13</td>
<td>70 (43–85)</td>
</tr>
<tr>
<td>Prothrombin ratio (%)</td>
<td>68</td>
<td>76±16.7</td>
<td>78 (29–100)</td>
</tr>
<tr>
<td>Pro-BNP (pg/ml)</td>
<td>60</td>
<td>2,289.9±5,502.3</td>
<td>403.5 (13–27,067)</td>
</tr>
<tr>
<td>pH</td>
<td>86</td>
<td>7.40±0.08</td>
<td>7.42 (7.13–7.58)</td>
</tr>
<tr>
<td>PaCO₂ (mm Hg)</td>
<td>86</td>
<td>36.4±9.4</td>
<td>36 (15.9–62)</td>
</tr>
<tr>
<td>PaO₂ (mm Hg)</td>
<td>86</td>
<td>74.4±28.4</td>
<td>68 (37–160)</td>
</tr>
<tr>
<td>HCO₃⁻ (mmol/L)</td>
<td>86</td>
<td>23.1±4.7</td>
<td>23 (8.2–38)</td>
</tr>
<tr>
<td>PaO₂/FiO₂ ratio</td>
<td>86</td>
<td>105.7±60.8</td>
<td>86 (37–338)</td>
</tr>
<tr>
<td>Urea (mmol/L)</td>
<td>91</td>
<td>12.3±9.3</td>
<td>9.7 (1–59.6)</td>
</tr>
<tr>
<td>Creatinine (μmol/L)</td>
<td>92</td>
<td>107±98.5</td>
<td>79.5 (37–759)</td>
</tr>
<tr>
<td>Iron (μmol/L)</td>
<td>60</td>
<td>10±6.6</td>
<td>7.7 (3.4–32)</td>
</tr>
<tr>
<td>Ferritin (μg/L)</td>
<td>56</td>
<td>1,063±638.9</td>
<td>922 (159–2,000)</td>
</tr>
<tr>
<td>Procalcitonin (μg/L)</td>
<td>65</td>
<td>1.53±5.89</td>
<td>0.25 (0.01–46.0)</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>64</td>
<td>134±152</td>
<td>92.5 (7–413)</td>
</tr>
<tr>
<td>SChE activity (UI/L)</td>
<td>78</td>
<td>5,857±1,773</td>
<td>5,794 (1,926–10,190)</td>
</tr>
</tbody>
</table>

ICU: intensive care unit; SD: standard deviation; WBC: white blood cell; AST: aspartate aminotransferase; ALT: alanine aminotransferase; Pro-BNP: pro-brain natriuretic peptide; PaCO₂: arterial carbon dioxide tension; PaO₂: arterial oxygen tension; HCO₃⁻: bicarbonate; FiO₂: fractional inspired oxygen; SChE: serum cholinesterase.
associated with death in univariate analyses were antecedent arterial hypertension, severe respiratory distress, and the presence of neurological impairment. Table 4 shows all the factors associated with death in univariate analysis. In our study, SChE activity greater than 5,000 UI/L during ICU stay was associated with a good outcome with 76% sensitivity and 79% specificity and an area under the curve (AUC) of 0.77 (Figure 1). Figure 2 shows the lowest SChE activity value (poor value) recorded in all patients during ICU stay according to outcomes. A CRP value greater than 180 mg/L was associated with a poor outcome with a sensitivity of 60% and specificity of 79% with an AUC of 0.73 (Figure 3).

Finally, multivariate analysis showed that factors associated with poor outcome were the development of acute renal failure (ARF; OR, 6.7), the use of mechanical ventilation (OR, 5.8), and SChE activity lower than 5,000 UI/L (OR, 5.0) (Table 5).

### DISCUSSION

**Principal Findings**

Our study confirms that severe cases of COVID-19 are characterized by acute respiratory distress, and the most common cause of death is refractory hypoxemia. Within the study period, 47 of our 96 patients died (49%). Despite the non-use of specific treatments (antiviral agents) [19] in our ICU, the mortality rate of 49% was similar to those reported in other studies [15-18,20,21], particularly in developed countries [22-24].

| Table 4. Factors associated with death in univariate analysis |
|---------------------|--------|------------------|------|
| Risk factor                      | Non-survivor (n=47) | Survivor (n=49) | P-value |
| Age (yr)                     | 65.5±12.3         | 59.3±12.6        | 0.016 |
| Arterial hypertension (comorbidity) | 29 (62)          | 19 (38.8)        | 0.025 |
| Decompensated diabetes       | 23 (24)           | 12 (12.5)        | 0.008 |
| Shock on ICU admission        | 12 (12.5)         | 2 (2.1)          | 0.003 |
| Invasive mechanical ventilation | 35 (36.5)       | 3 (3.1)          | <0.001 |
| Noninvasive ventilation       | 36 (37.5)         | 12 (12.5)        | <0.001 |
| Bacterial nosocomial infection | 26 (27.1)        | 2 (2.1)          | <0.001 |
| Kidney failure                | 37 (38.5)         | 14 (14.6)        | <0.001 |
| Hypernatremia                 | 10 (10.4)         | 1 (1)            | 0.002 |
| Hyperkalemia                  | 14 (14.6)         | 2 (2.1)          | <0.001 |
| SpO₂ under air room (without O₂) | 55±19            | 70±18            | 0.001 |
| Respiratory rate (breaths/min) | 33±15            | 27±9             | 0.026 |
| Heart rate (beats/min)        | 97±22             | 85±19            | 0.008 |
| Glasgow coma scale            | 12.5±4.2          | 14.5±1.8         | 0.003 |
| SOFA score                    | 6±3.5             | 3.8±1.9          | <0.001 |
| SAPS II score                 | 39.4±18.3         | 27.9±11          | <0.001 |
| White blood cell (cells/mm³)  | 14,627±6,393      | 11,814±5,315     | 0.027 |
| Urea (mmol/L)                 | 15±12.2           | 9.8±4.5          | 0.011 |
| Creatinine (µmo/L)            | 129.5±134.1       | 86.5±32.5        | 0.046 |
| SChE activity (UI/L) on ICU admission | 5,471±1,723 | 6,242±1,763 | 0.082 |
| CRP (mg/L) on ICU admission   | 166±196           | 104±86           | 0.074 |
| Lowest SChE activity (UI/L)   | 4,574±1,821       | 6,059±1,628      | <0.001 |
| Highest CRP value (mg/L)      | 224±129.5         | 127.5±92.5       | <0.001 |
| pH                            | 7.31±0.09         | 7.43±0.04        | <0.001 |
| PaO₂/FiO₂ ratio on ICU admission | 92.2±44.8       | 117.1±70.2       | 0.020 |
| Lowest PaO₂/FiO₂ ratio        | 68.8±25.9         | 97.2±59.9        | 0.008 |
| Lowest HCO₃⁻ (mmol/L)         | 19.3±5.8          | 21.5±4.0         | 0.049 |

Values are presented as mean±standard deviation or number (%). ICU: intensive care unit; SpO₂: oxygen saturation measured by pulse oximetry; SOFA: Sequential Organ Failure Assessment; SAPS: Simplified Acute Physiology Score; SChE: serum cholinesterase; CRP: C-reactive protein; PaO₂: arterial oxygen tension; FiO₂: fractional inspired oxygen; HCO₃⁻: bicarbonate.
Management of Severe COVID–19 Infection

In our ICU, we use corticosteroids (dexamethasone, 12–24 mg/day), which are known for their ability to regulate a number of cytokines, to treat SARS-CoV-2-infected patients [16]. Acute respiratory distress was treated via high-flow nasal oxygen or facial mask. Nonetheless, severe cases in urgent need of supportive care, namely those suffering from acute hypoxemia, had to be placed under invasive and/or NIV. As recommended [19,25], zinc, vitamin D and vitamin C, diuretics (in the absence of hypovolemia and/or shock), and enoxaparin were administered to all patients if there were no contraindications. In fact, there is some evidence that deficiency of one or more of these three elements (zinc, vitamin D, vitamin C) compromises the immune response, making an individual more vulnerable to viral infections and to a worse disease prognosis [25]. We did not use hydroxychloroquine to treat patients admitted to our ICU following severe respiratory distress due to COVID-19 based on the results of many studies [20,21,26] and the World Health Organization. However, we used the prone position to treat COVID-19 patients who were not intubated and those with severe respiratory failure and hypoxemia. In fact, it has been established that the timely use of the prone position in patients with a COVID-19 infection suffering from severe hypoxemia can improve oxygenation and prevent the need for IMV, ultimately decreasing the number of COVID-19 patients who die due to complications of severe hypoxemia [27].
Clinical Outcomes

The high mortality rate (49%) observed in our study, although somewhat similar to those reported in other studies [15-18], particularly in developed countries [22-24], can be explained by several factors. First, 78 patients (81%) had one or more comorbidities with a median age of 64 years. Moreover, on ICU admission, clinical examination showed that all patients exhibited major signs of respiratory distress and chest CT scans showed parenchymal opacification with more than 50% involvement in more than 81% of cases. Moreover, 36 patients (37.5%) required vasopressors during their ICU stay. In the current study, we found that the development of ARF was associated with a poor outcome.

Our study confirms the results of several previous studies [28,29] that reported that the development of ARF was strongly associated with severe clinical outcomes and mortality. In fact, patients with COVID-19 with ARF had a 3-fold higher odds of death than COVID-19 patients without ARF, and a 4-fold higher odds of death than ARF due to other causes [30]. Moreover, we found in the current study that SChE activity lower than 5,000 UI/L was associated with a poor outcome in multivariate analysis. Our results confirm the results of a recent study performed by Nakajima et al. [31] who found that cholinesterase level on admission was an independent predictor of the severity of COVID-19 pneumonia and mortality. In fact, cholinesterase activity is thought to be affected by acute-phase infections and inflammatory processes [32]. Cholinesterase inhibition can be caused by inflammatory mediators (cytokines) released in severe cases of COVID-19 pneumonia. In the current study, only 28 patients (29%) developed nosocomial infections. Despite the lower rate of nosocomial infections reported (40.7%) in an earlier study [33], it is within the range reported in other studies (15%–40%) [34,35].

Study Limitations

Our study had several limitations. First, its retrospective nature is a methodological limitation, as all retrospective studies suffer from incomplete information. In our study, CRP and PCT levels and SChE activity were not assessed in all patients admitted to the ICU. Moreover, SChE activity was not measured at the same time point in all patients. In addition, because of a lack of equipment, extracorporeal membrane oxygenation was used in only one patient among 38 mechanically ventilated patients. Finally, we did not follow-up patients after ICU discharge. However, this study is one of the first to study the clinical manifestations, management, and outcomes of patients with severe COVID-19 infection requiring ICU admission in Africa.

In this retrospective cohort study of critically ill patients admitted to the ICU in Sfax, Tunisia, for acute respiratory failure following COVID-19 infection, the mortality rate was high. The development of ARF, the use of mechanical ventilation, and SChE activity lower than 5,000 UI/L were associated with poor outcomes. Further studies are needed on this subject.

CONFLICT OF INTEREST

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

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AUTHOR CONTRIBUTIONS


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Diaphragm ultrasound as a better predictor of successful extubation from mechanical ventilation than rapid shallow breathing index

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1Department of Critical Care Medicine, Imperial Hospital, Chattogram; 2Department of Public Health, North South University, Dhaka; 3Department of Anaesthesia and Intensive Care Medicine, Chattogram Medical College Hospital, Chattogram, Bangladesh

Background: In 3%–19% of patients, reintubation is needed 48–72 hours following extubation, which increases intensive care unit (ICU) morbidity, mortality, and expenses. Extubation failure is frequently caused by diaphragm dysfunction. Ultrasonography can be used to determine the mobility and thickness of the diaphragm. This study looked at the role of diaphragm excursion (DE) and thickening fraction in predicting successful extubation from mechanical ventilation.

Methods: Thirty-one patients were extubated with the advice of an ICU consultant using the ICU weaning regimen and diaphragm ultrasonography was performed. Ultrasound DE and thickening fraction were measured three times: at the commencement of the T-piece experiment, at 10 minutes, and immediately before extubation. All patients' parameters were monitored for 48 hours after extubation. Rapid shallow breathing index (RSBI) was also measured at the same time.

Results: Successful extubation was significantly correlated with DE (P<0.001). Receiver curve analysis for DE to predict successful extubation revealed good properties (area under the curve [AUC], 0.83; P<0.001); sensitivity, 77.8%; specificity, 84.6%; positive predictive value (PPV), 84.6%; negative predictive value (NPV), 73.3% while cut-off value, 11.43 mm. Diaphragm thickening fraction (DTF) also revealed moderate curve properties (AUC, 0.69; P=0.06); sensitivity, 61.1%; specificity, 84.6%; PPV, 87.5%; NPV, 61.1% with cut-off value 22.33% although former one was slightly better. RSBI could not reach good receiver operating characteristic value at cut-off points 100 breaths/min/L (AUC, 0.58; P=0.47); sensitivity, 66.7%; specificity, 53.8%; PPV, 66.7%; NPV, 53.8%).

Conclusions: To decrease the rate of reintubation, DE and DTF are better indicators of successful extubation. DE outperforms DTF.

Key Words: airway extubation; diaphragm excursion; diaphragm thickening fraction; rapid shallow breathing index; ventilator weaning

INTRODUCTION

Extubation failure is linked with a high mortality rate and adverse consequences such as aspiration, atelectasis, and pneumonia [1]. Therefore, before extubating a patient on artificial ventilation, the physician must determine whether they can breathe independently. This determination is made based on the results of a spontaneous breathing trial (SBT) using a...
T-piece or low-level pressure support. If the patient can spontaneously breathe, the physician must determine if the patient can undergo extubation [2]. Intensivists use four distinct methods when doing the SBT: (1) T-piece trial, in which only supplementary oxygen is delivered through a T-piece linked to an endotracheal tube; (2) continuous positive airway pressure (CPAP) trial, in which CPAP is set to the same level as the prior positive end-expiratory pressure (PEEP); (3) spontaneous trial with invasive ventilation with inspiratory pressure augmentation; and (4) automatic tube compensation [3].

Continuous or repetitive monitoring of vital parameters is required in these patients, and a combination of subjective and objective criteria is typically used to determine disease reversal. Oxygenation, hemodynamic status, acid-base balance, renal function, nutrition, and gastrointestinal function are monitored continuously or repetitively. However, it has been shown that assessing respiratory muscles, especially the diaphragm is inadequate in everyday intensive care unit (ICU) practice [4]. There is growing recognition that diaphragm weakening is prevalent in patients undergoing mechanical ventilation (MV) and is almost certainly a factor in extubation failure [5]. Recent researches indicate that the ventilator is likely to be the source of the reduced diaphragm force-generating capacity seen in mechanically ventilated patients, a condition called ventilator-induced diaphragmatic dysfunction [6,7].

Weaning predictors are factors used to assist doctors in determining whether or not extubation efforts will be effective. Although an international consensus meeting in 2005 recommended against their regular use in clinical decision-making, researchers did not abandon the use [3]. Nevertheless, some individuals who do not meet all requirements are ultimately weaned [8]. It is estimated that 40% of the time of MV is spent on weaning to extubate the patients effectively [3]. Numerous weaning indices have been evaluated to determine the optimum weaning timeframe to avoid reintubation. Among these, the rapid shallow breathing index (RSBI) has gained widespread usage owing to its simplicity of computation and avoidance of complicated pulmonary mechanics calculations [9]. However, there are limitations in using RSBI to predict successful extubation as it does not consider the independent contribution of the diaphragm and is influenced by the accessory muscles of respiration [9]. There are also other predictors of successful extubation. These include respiratory rate alone, vital capacity, tidal volume per kilogram of body weight, airway occlusion pressure at 0.1 seconds, and an integrated evaluation of dynamic compliance, respiratory rate, oxygenation, and maximum inspiratory pressure, referred to as the CROP (compliance, rate, oxygenation, and pressure) index, as well as other integrated weaning indices that utilize dynamic analogs. But all of them are influenced by different clinical states and have different cut-off values, sensitivities, and specificities. Respiratory rate can be increased by distress, pain, and acidosis and reduced by sedation and muscle paralysis, so it may not accurately reflect respiratory muscle strength and load. Vital capacity cannot be accurately measured in many clinical situations, such as reduced patient consciousness. Maximum inspiratory pressure has a significant disadvantage due to different measurement methods, which can give different values in other patients due to the use of analog or digital vacuum manometers [10].

The most often seen reason for extubation failure is diaphragmatic dysfunction, which increases over time while the patient is on MV [11]. So a single predictor which can be applicable in a wide range of clinical states and also gives an accurate picture of the activity of the diaphragm can help in predicting extubation failure. Ultrasound of the diaphragm is a non-invasive, straightforward procedure that is highly reproducible in the same individuals. As a result of its extensive usage, several criteria for diaphragmatic ultrasonography have been defined, including diaphragm excursion (DE) and diaphragm thickening fraction (DTF) [12]. Other diaphragmatic assessment techniques, such as fluoroscopy, phrenic nerve conduction, and trans-diaphragmatic pressure measurements, have limitations and drawbacks, particularly in the ICU, due to ionizing radiation exposure, lack of widely available methods in practice, and the requirement for patient transportation to the radiology department investigation room [13,14].

Successful extubation to prevent reintubation is critically important to reduce mortality, morbidity, and expense of the patients. Among the conventional parameters, RSBI has gained the highest predictability, but its accuracy has been questioned. Since The diaphragm, the primary respiratory

**KEY MESSAGES**

- Diaphragm ultrasonography (diaphragm excursion and diaphragm thickening fraction) is a better tool to predict successful extubation compared to rapid shallow breathing index.
- Among these two parameters, diaphragm excursion is a better predictor than diaphragm thickening fraction.
When the ICU consultant took the extubation decision. Just the patient was taken by the ICU consultant. We were informed the decision to discontinue SBT and reintubation of the study comprised a total of 31 intubated patients who were assessed for eligibility and 33 of them met the inclusion criteria and their attendant provided informed written consent. But two patients died after enrollment, therefore, this study comprised a total of 31 intubated patients who were scheduled to be extubated according to their protocol.

Patients aged >18 years who had an adequate cough, no excessive tracheobronchial secretion, resolution of an underlying critical illness for which the patient was intubated & was alert and cooperative without sedatives, hemodynamic stability (i.e., heart rate 140 bpm, mean arterial pressure >65 mm Hg without or with the lowest dose of vasopressors), stable metabolic status, and improved respiratory function: arterial oxygen saturation (SaO₂) >90% on fractional inspired oxygen (FiO₂) 0.4 or partial pressure of oxygen (PaO₂)/FiO₂ >150 mm Hg, PEEP 8 cm H₂O, respiratory rate 35 bpm and without respiratory acidosis was included in this study. Patients having a history of diaphragm illness, cervical spine damage, neuromuscular disorders, a current thoracostomy, pneumothorax, pneumomediastinum, or any skin breach prohibiting ultrasound tests, or phrenic nerve palsy and patients’ attendants refusing written consent was excluded from the research.

Study Procedure
The decision to discontinue SBT and reintubation of the patient was taken by the ICU consultant. We were informed when the ICU consultant took the extubation decision. Just at the start of 30 minutes of T-piece trial and after 10 minutes, right DE and DTF were evaluated using Sonosite M-Turbo (FUJIFILM Sonosite, Bothell, WA, USA) ultrasonography machine with the patient in semirecumbent position with the bed elevated between 20º and 40º. Measurement of DE and DTF was recorded in a data sheet. RSBI was also simultaneously calculated at the bedside. The same procedure was done just before extubation. ICU consultant was unaware of ultrasound results. Three measurements were taken during the T-piece trial and were averaged.

When the patient passed the 30 minutes of T-piece trial without deterioration, extubation was done by ICU consultant and received oxygen through nasal cannula patient was followed up for 48 hours post-extubation with regular checking of vital parameters and accordingly the post-extubation protocol to monitor the patient of the ICU of study institute. Extubation success is defined as the continuation of spontaneous breathing for at least 48 hours after extubation. Extubation failure was defined as the inability to breathe spontaneously for at least 48 hours without the assistance of a ventilator. For the patients who needed reintubation, their DE and DTF measurement measured during the T-piece trial was correlated with RSBI.

Diaphragm ultrasonic measurements were obtained in both brightness (B) and motion (M) mode on the right subcostal side. We utilized a high-resolution linear probe operating at 13-6 MHz and a curvilinear probe operating at 5-2 MHz to determine the diaphragm thickness (DT) and DE in both B and M modes. According to the inclusion criteria, all patients were measured in the semirecumbent posture with the head of the bed raised between 20º and 40º. A 5-2 MHz ultrasonic probe is used to determine the right DE. The probe is positioned directly under the right costal edge along the mid-clavicular line and directed medially, cephalad, and dorsally such that the ultrasonic beam reaches the posterior part of the diaphragm perpendicularly. The liver serves as an acoustic window for the body. To begin, B-mode is utilized to get the best picture possible and to choose the exploration line.

Then, M-mode is used to see the diaphragm’s motion along the chosen line. The normal diaphragm contracts and travels caudally toward the probe during inspiration; during expiration, the normal diaphragm contracts and moves cranially away from the probe; this is recorded as an upward motion of the M-mode tracing. The vertical axis of the tracing is used to quantify the DE from the baseline to the point of greatest inspiration height on the picture. Three measurements were taken, and the average was calculated.

MATERIALS AND METHODS
The study was approved by the Ethical Review Board (No. CMC/PG/2019/57) of the Chattogram Medical College Hospital, Chattogram, Bangladesh. Written informed consent was obtained from the patient’s attendant.

Study Participants
From September 2019 to August 2020, this longitudinal observational research was conducted in the adult ICU of a tertiary level hospital in Bangladesh. During this period, 189 patients were assessed for eligibility and 33 of them met the inclusion criteria and their attendant provided informed written consent. But two patients died after enrollment, therefore, this study comprised a total of 31 intubated patients who were scheduled to be extubated according to their protocol.

Patients aged >18 years who had an adequate cough, no excessive tracheobronchial secretion, resolution of an underlying critical illness for which the patient was intubated & was alert and cooperative without sedatives, hemodynamic stability (i.e., heart rate 140 bpm, mean arterial pressure >65 mm Hg without or with the lowest dose of vasopressors), stable metabolic status, and improved respiratory function: arterial oxygen saturation (SaO₂) >90% on fractional inspired oxygen (FiO₂) 0.4 or partial pressure of oxygen (PaO₂)/FiO₂ >150 mm Hg, PEEP 8 cm H₂O, respiratory rate 35 bpm and without respiratory acidosis was included in this study. Patients having a history of diaphragm illness, cervical spine damage, neuromuscular disorders, a current thoracostomy, pneumothorax, pneumomediastinum, or any skin breach prohibiting ultrasound tests, or phrenic nerve palsy and patients’ attendants refusing written consent was excluded from the research.

Study Procedure
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The DTF was determined using a 10-MHz linear ultrasound probe in the diaphragm and rib cage zone between the eighth and tenth intercostal spaces. The ultrasound picture is turned into a B-mode image. This region sees the diaphragm as a three-layer structure composed of two parallel echoic lines (the diaphragmatic pleura and the peritoneal membrane) and a hypoechoic structure in between (the muscle itself). At the end of expiration and inspiration, the picture was frozen. The DT on frozen images is the distance between the center of the pleural line and the middle of the peritoneal line. On the same scan, the DT was measured three times, and the results were averaged. The DTF was calculated as follows: DTF=(thickness at end inspiration–thickness at end-expiration)/thickness. The DTF was computed for each subject as the mean of the measured values. RSBI was collected concurrently with right DE and DTF measurements.

**Statistical Analysis**

Categorical data were presented as frequency & relative frequency. The association between extubation outcome and RSBI, DE, DTF was analyzed using an independent sample t-test. Receiver operating characteristic (ROC) curves were used to assess the DE, DTF, and RSBI to predict successful extubation. Sensitivity and specificity were also analyzed to determine appropriate cut-off values of DE, DTF, and RSBI. Differences of the area under ROC curves were compared using the non-parametric method. A two-tailed P-value <0.05 is considered statistically significant. All statistical analyses were performed using Stata ver. 16 (StataCorp., College Station, TX, USA).

**RESULTS**

The baseline characteristics of the patients are presented in Table 1. Of the 31 patients, the majority were above 50 years of age (35%) and male (63%). Hypertension (45%), chronic obstructive pulmonary disease (32%), and diabetes (29%) were the predominant comorbidities, while 45% of the patients had no comorbidity. The patients were under invasive MV for an average of 11 days (standard deviation, 0.81) before the weaning trial. Eighteen patients (58%) were successfully extubated, and 13 (42%) needed reintubation. Of those who needed reintubation, most of them were required in 12 hours (19%).

Table 2 presents the bivariate relationship between baseline and clinical parameters with extubation outcome. Patients with no comorbidity and a shorter duration of stay in MV were more likely to be extubated successfully. DE and DTF also showed a highly significant association, respectively, with successful extubation, whereas RSBI had no significant association.

The ROC curve for RSBI, DE and DTF is depicted in Figure 1. The area under the curve (AUC) for DE was high (0.83), and the P-value was highly significant (<0.001). Both lower and upper bound area was also above the area of 0.5 indicating that DE could accurately predict the successful extubation. The AUC of DTF and RSBI was 0.69 (95% confidence interval [CI], 0.49–0.88) and 0.58 (95% CI, 0.36–0.80). Since the lower bound of the 95% confidence interval was below 0.5 for these two parameters with insignificant P-value (DTF, P=0.06 and RSBI, P=0.47), they are poor predictors of successful extubation outcome. However, DTF is very close to a significant level. Table 3 represents the cut-off value, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for RSBI, DE, and DTF.

**DISCUSSION**

In this study, it is found that DE has a significant association
Table 2. Comparison of baseline and clinical parameters according to extubation outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>Successful extubation (n=18)</th>
<th>Failed extubation (n=13)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>38±14</td>
<td>48±17</td>
<td>0.07</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>0.59</td>
</tr>
<tr>
<td>Male</td>
<td>10 (53)</td>
<td>9 (47)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>8 (67)</td>
<td>4 (33)</td>
<td></td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>No comorbidity</td>
<td>11 (78.57)</td>
<td>3 (21.43)</td>
<td></td>
</tr>
<tr>
<td>One or more comorbidity</td>
<td>7 (41.18)</td>
<td>10 (58.82)</td>
<td></td>
</tr>
<tr>
<td>Duration of stay in mechanical ventilation (day)</td>
<td>8.67±2.74</td>
<td>14.62±4.33</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RSBI (breaths/min/L)</td>
<td>100.46±2.84</td>
<td>99.49±3.71</td>
<td>0.41</td>
</tr>
<tr>
<td>DE (mm)</td>
<td>12.41±2.38</td>
<td>9.20±1.87</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DTF (%)</td>
<td>22.34±2.73</td>
<td>14.74±6.89</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation or number (%). RSBI: rapid shallow breathing index; DE: diaphragm excursion; DTF: diaphragm thickening fraction.

Table 3. Sensitivity, specificity, PPV, and NPV of RSBI, DE, and DTF to predict successful extubation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cut-off</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSBI (breaths/min/L)</td>
<td>100</td>
<td>66.7</td>
<td>53.8</td>
<td>66.7</td>
<td>53.8</td>
</tr>
<tr>
<td>DE (mm)</td>
<td>11.43</td>
<td>77.8</td>
<td>84.6</td>
<td>87.5</td>
<td>73.3</td>
</tr>
<tr>
<td>DTF (%)</td>
<td>22.33</td>
<td>61.1</td>
<td>84.6</td>
<td>84.6</td>
<td>61.1</td>
</tr>
</tbody>
</table>

PPV: positive predictive value; NPV: negative predictive value; RSBI: rapid shallow breathing index; DE: diaphragm excursion; DTF: diaphragm thickening fraction.

Figure 1. Comparison of receiver operating characteristic (ROC) curve for diaphragm excursion (DE), diaphragm thickening fraction (DTF), and rapid shallow breathing index (RSBI). Area under the ROC curves for DE: 0.83 (95% confidence interval [CI], 0.68–0.99), for DTF: 0.69 (95% CI, 0.49–0.88), and for RSBI: 0.58 (95% CI, 0.36–0.80).

with extubation success. DE predicted successful extubation in this study which matched with several studies [15-17]. DE showed excellent properties in the ROC curve. The AUC was 0.83 with significant value, while cut-off value 11.43 mm, sensitivity revealed 77.8%, specificity 84.6%, PPV 87.5% and NPV 73.3%. Similar result was found in the study of Spadaro et al. [18] with cut-off value of ≤14mm, AUC, 0.82, sensitivity, 88.2%, specificity, 61.8%, PPV, 53.6% and NPV, 91.3% [18]. Farghaly and Hasan [19] evaluated diaphragmatic parameters (DT, DTF and DE) in 54 patients who successfully passed SBT. He found a sensitivity of 87.5% and specificity of 71.2% when the cut-off value of DE was ≥10.5 mm with AUC 0.879.

Osman and Hashim [16] found a cut-off value of 10 mm; sensitivity, 83.3%; specificity, 100%; NPV, 94.3%; and PPV, 100%. DTF was not significantly correlated with successful extubation in this study but very close to a significant level. However, it was found significant in some. The DTF scores showed good properties with AUC 0.706; cut-off value, 19.77; sensitivity, 58.8%; specificity, 77.8%; PPV, 83.3%; and NPV, 50.0% in this study. A better result was observed about DTF in the study of Osman and Hashim [16], with a 28% cut-off value showed 88.9% sensitivity, 100% specificity, 96.2% NPV, and 100% PPV. Osman and Hashim [16] investigated and wrote a review article on the efficacy of DTF where he explained that cut-off for DTF varied 30–34 and sensitivity varied 88%–90%, and specificity ranged 61%–82%. The insignificant correlation of DTF with successful extubation in this study is due to the low sample size. Zambon et al. [20] stated a lack of data.
about the learning curve to measure the thickening fraction to operator-dependent variations, which influence the measurements.

RSBI was shown to be a poor predictor of extubation success in our study. Karthika et al. [9] showed that the RSBI should not be used generally to predict effective extubation. Danaga et al. [21] discovered that the conventional RSBI cut-off value (105 breaths/min/L) accurately predicted just 20% of extubation failures. According to Boutou et al. [22], RSBI measurements taken early in an SBT cannot correctly predict successful extubation. RSBI is not a reliable predictor of effective extubation in neurosurgical patients, as discovered by Vidotto et al. [23]. According to Verceles et al. [24], isolated RSBI measures do not reliably predict successful extubation in patients requiring prolonged MV. According to Teixeira et al. [25], serial RSBI measurements throughout 120 minutes of SBT were unable to identify extubation failure in patients who had previously had a successful SBT with an initial RSBI of 105 breaths/min/L. According to Shah et al. [26], RSBI does not vary substantially throughout a 90-minute SBT during the trial.

In a study, Spadaro et al. [18] found that DE is better than RSBI. Another study by Dinino et al. [27] found that the DTF is better than RSBI. This study found that both DE and DTF were better at predicting successful extubation than RSBI, as the former had better ROC properties. Among these two parameters, DE is better than DTF.

Ultrasonography can help diagnose diaphragm dysfunction and determine whether or not extubation will be successful. DE and DTF can therefore be useful parameters in predicting extubation success. Among these two, DE outperformed DTF in predicting successful extubation outcomes.

Since this study is single-centric with a small sample size, the results may not be generalizable, and selection bias cannot be ruled out completely. Furthermore, we did not compare diaphragm strength to sonographic findings by magnetic phrenic nerve stimulation, which is considered the gold standard [28].

Ultrasonography-based diaphragm measurements, mainly DE and DTF, are significant predictors of successful extubation than traditional parameters like RSBI. So it should be routinely done in the ICU. Future studies in multiple centers with larger sample sizes should be conducted to verify the results.

**CONFLICT OF INTEREST**

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

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Conceptualization: MJA. Data curation: FKP. Formal analysis: MAI, SR. Methodology: MJA, SC. Project administration: MJA, KIN. Visualization: MJA, KIN. Writing–original draft: MJA, SR. Writing–review & editing: RKN, HOR.

**REFERENCES**


The feasibility and safety of percutaneous dilatational tracheostomy without endotracheal guidance in the intensive care unit

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Background: Percutaneous dilatational tracheostomy (PDT) is a common procedure in intensive care units (ICUs). Although it is thought to be safe and easily performed at the bedside, PDT usually requires endotracheal guidance, such as bronchoscopy. Here, we assessed the clinical outcomes and safety of PDT conducted without endotracheal guidance.

Methods: In the ICU and coronary ICU at a tertiary hospital, PDT was routinely performed without endotracheal guidance by a single medical intensivist using the Griggs technique PDT kit (Portex Percutaneous Tracheostomy Kit). We retrospectively reviewed the electronic medical records of patients who underwent PDT without endotracheal guidance.

Results: From January 1 to December 31, 2018, 78 patients underwent PDT without endotracheal guidance in the ICU and coronary ICU. The mean age of these subjects was 71.9±11.5 years, and 29 (37.2%) were female. The mean Acute Physiology and Chronic Health Evaluation (APACHE) II score was 25.9±5.8. Fifty patients (64.1%) were on mechanical ventilation during PDT. Failure of the initial PDT attempt occurred in four patients (5.1%). In two of them, PDT was aborted and converted to surgical tracheostomy; in the other two patients, PDT was reattempted after endotracheal reintubation, with success. Minor bleeding at the tracheostomy site requiring gauze changes was observed in five patients (6.4%). There were no airway problems requiring therapeutic interventions or procedure-related sequelae.

Conclusions: PDT without endotracheal guidance can be considered safe and feasible.

Key Words: airway management; intensive care units; tracheostomy

INTRODUCTION

Percutaneous dilatational tracheostomy (PDT) is commonly performed for the airway management of critically ill patients in the intensive care unit (ICU) [1-3]. Although the timing of tracheostomy in ventilated patients is a controversial topic [4,5], tracheostomy has many advantages in facilitating weaning, improving patient mobilization and reducing sedative requirements, laryngeal damage, breathing effort, and costs [6,7].

Although surgical tracheostomy is the routine practice of choice, PDT is also widely performed in the ICU [1,3]. Endoscopic guidance with bronchoscopy was the standard of prac-
tice at initial introduction because of its direct visualization of the endotracheal position [8]. Physicians have performed PDT by a variety of endotracheal guides, such as bronchoscopy [9], real-time ultrasound [10,11], and light sources [12]. In a recent study, PDT was safely performed by experienced physicians both with and without bronchoscopic guidance [13]. Additionally, Pattnaik et al. [14] reported a case series of 300 patients who safely underwent PDT without bronchoscopic guidance. The purpose of this study was to analyze the feasibility and safety of PDT without endotracheal guidance at the bedside in the ICU.

MATERIALS AND METHODS

Research Ethics
This study was approved by the Institutional Review Board of Dong-A University Hospital (IRB No. DAUHIRB-20-036). The Board waived the requirement for informed consent due to the retrospective study design.

Study Design and Patient Selection
This was a retrospective observational study of patients who underwent PDT without endotracheal guidance at a single tertiary hospital from January 1 to December 31, 2018. Patients who underwent PDT were initially screened, and the corresponding electronic medical records, including procedure notes, nurse notes, vital signs, and physician progression notes, were manually reviewed.

Patients ≥18 years of age were included if they underwent PDT without endotracheal guidance, which was an almost routine practice for tracheostomy during the period. Patients were excluded if PDT was performed by other physicians or by endotracheal guidance (bronchoscopy, video laryngoscopy, ultrasound, etc.) and if they initially underwent surgical tracheostomy.

Outcome Measurements
The primary outcome was defined as successful PDT. PDT failure was defined as reintubation or airway management using a supraglottic airway device (SAD) for any reason or conversion to surgical tracheostomy after the initiation of PDT. Secondary outcomes were defined as immediate (within 24 hours) and delayed (within 7 days) procedure-related complications, such as hypoxia, bleeding and hypotension within 24 hours after PDT and delayed problems associated with tracheostomy within 7 days after PDT. Hypotension was defined as a systolic blood pressure of 70 mm Hg or less; major bleeding was defined as bleeding requiring an aggressive intervention, such as embolization, electrocoagulation, and wound revision; and minor bleeding was defined as hemorrhage requiring direct compression at the procedure site within an hour. Hypoxia was defined an oxygen saturation on pulse oximetry of 88%. Survival and discharge were also reviewed.

Procedure
PDT was routinely performed by a single medical intensivist using the Griggs technique PDT kit (Portex Percutaneous Tracheostomy Kit; Smith Medical, Kent, England) without any endotracheal guidance. The physician in this study, as a medical intensivist, had experience with more than 100 cases of PDT for more than 3 years and performed PDT with bronchoscopic endotracheal guidance in 20 cases and without endotracheal guidance in 52 cases in the previous 1 year.

The PDT procedures were routinely performed as follows. The patient was prepared by the administration of analgesics and sedatives and was placed in the supine position with the neck hyperextended. Continuous remifentanil infusion from 0.06 µg/kg/hr to 0.14 µg/kg/hr was used for analgesia, and bolus 5 mg of midazolam was used for procedural sedation. A neuromuscular blockade agent was not used during PDT. Blood pressure, heart rate and pulse oximetry were continuously monitored. The neck of the patient was widely disinfected with chlorhexidine gluconate solution and covered with sterile drapes for the aseptic procedure. The operator palpated the neck carefully from top to bottom to identify two important landmarks: the cricothyroid membrane and the sternal notch. The incision site was placed under 1 fingerbreadth from the cricothyroid membrane, targeting between the 2nd and 3rd tracheal cartilaginous rings. The sternal notch was a landmark warning not to proceed below this line. Local anesthesia with 2% lidocaine and 1:100,000 epinephrine was given subcutaneously at the incision site. After making an approximately 2-cm transverse skin incision, dissection of the pretracheal soft tissue was performed. The assistant changed the fraction of in-
spired oxygen setting to 100% and withdrew the endotracheal tube to 15 cm on the incisor while the operator palpated the tracheal membrane at the insertion site. Puncture of the trachea was cautiously performed on the midline of the incision, and the endotracheal position was confirmed by air bubble aspiration of a syringe containing 0.9% normal saline. Then, a guide wire was inserted, followed by removal of the needle. The initial stoma was made using a dilator, followed by second stoma formation with dilating forceps by the Griggs technique. Then, the tracheostomy cannula was placed using the Seldinger technique along the guide wire, and the patient was totally extubated by the assistant. The proper endotracheal position of the tracheostomy tube confirmed the smooth passage of the rubber suction tip into the cannula. During the procedure, most events concerning the patient were recorded on the electronic medical record system. All patients were confirmed by chest X-rays, and vital signs were recorded after the procedure.

Statistical Analysis
The data were analyzed using IBM SPSS ver. 21.0 (IBM Corp., Armonk, NY, USA) for Windows. Nominal variables were examined by the Fisher’s exact test, and continuous variables were examined by the Shapiro-Wilk and the Kolmogorov-Smirnov test for assessing the normality of the distribution. If the test result was significant (P<0.05), the sample data distribution was considered non-normal. Over half of the continuous variables followed a normal distribution and are presented as the mean and standard variation. The other continuous variables followed a non-normal distribution and are presented as the median (interquartile range). Nominal variables are presented as the number and incidence rate (%). Values were rounded off to one decimal place.

RESULTS

Patient Characteristics
From January 1 to December 31, 2018, 78 patients underwent PDT in the ICU and coronary ICU. The mean age was 71.9±11.5 years, and 29 patients (37.2%) were female. More than half of the patients were admitted to pulmonology (46 patients, 59%), followed by cardiology (7 patients, 9%), nephrology (5 patients, 6.4%), and others (16 patients, 20.5%). The mean Acute Physiology and Chronic Health Evaluation (APACHE) II score was 25.9±5.8, and 71 patients (91%) had received mechanical ventilation during their whole hospitalization. Fifty patients (64.1%) had been on mechanical ventilation during PDT; ventilator modes were synchronized intermittent mandatory ventilation (35 patients, 44.9%), pressure support ventilation (9 patients, 11.5%), and controlled mandatory ventilation (6 patients, 7.7%). Their mean FiO₂ was 40.0% (30.0–40.0), and the duration from mechanical ventilation to PDT was 14.0±7.5 days. Seventeen patients (21.8%) needed vasopressors to maintain their blood pressure. Thirty patients (38.5%) had taken anticoagulants or antiplatelets within 7 days before PDT, and their mean duration was 2.0 days (2.0–3.3 days): aspirin (9 patients, 11.5%), clopidogrel (9 patients, 11.5%), enoxaparin (14 patients, 17.9%), heparin (3 patients, 3.8%), warfarin (3 patients, 3.8%), and dalteparin (1 patient, 1.3%). Detailed baseline characteristics of the patients are shown in Table 1.

Successful PDT and Complications Associated with PDT
Failure
The primary outcome of the study was successful PDT. Among the 78 study patients, successful PDT was achieved in 74 (94.9%) at the first cannulation attempt. Four patients experienced initial cannulation failure. In two of these patients, a
SAD was used to maintain airway patency, followed by successful PDT. The other two patients were reintubated and converted to surgical tracheostomy. All of the patients recovered completely after PDT or surgical tracheostomy without any hypoxia-related sequelae.

In the assessment of secondary outcomes, hypotension was the most common complication (16 patients, 20.5%); eight patients (10.3%) required crystalloid replacement only, four patients (5.1%) required vasopressors, and four patients (5.1%) required both crystalloid replacement and vasopressors. Minor bleeding at the tracheostomy site occurred in five patients (6.4%), and they needed only supportive care, such as direct manual compression or simple dressing. Major bleeding requiring surgical intervention or transfusion was not reported (Table 2). There were no early complications concerning the airway requiring therapeutic procedures or interventions within a week after the procedure.

After PDT, 47 patients (60.3%) were transferred to another hospital, five patients (6.4%) were discharged home, and 26 patients (33.3%) died. The mean time from the day of PDT to death was 23.0 days (11.3–67.0 days) (Table 3).

**Clinical Characteristics of Patients with PDT Failure on the First Attempt**

Four patients failed at the first attempt of PDT due to hypoxia. Clinical characteristics of patients with initial PDT failure are described in Table 4. Four patients experienced failed weaning from mechanical ventilation for various reasons and underwent PDT after different durations of mechanical ventilation. In the first case of failure, a 65-year-old woman with non-small-cell lung carcinoma needed mechanical ventilation due to consistent atelectasis and pneumonia. The 1st PDT attempt failed, and the SpO2 dropped to 67% during the 1st attempt. A SAD was inserted for oxygenation, and the 2nd PDT attempt was successful. In the second case, a 59-year-old man with olivopontocerebellar atrophy required long-term mechanical ventilation due to postoperative complications of gastric ulcer perforation. After the 1st PDT attempt, the mechanical ventilator was connected, but the tidal volume was not received from the mechanical ventilator due to tracheostomy site obstruction. The patient’s SpO2 dropped to 76%, and a SAD was inserted immediately; the 2nd PDT attempt was successful. In the third case, a 48-year-old woman with alcoholic liver cirrhosis failed to wean from mechanical ventilation after liver transplantation. The 1st PDT attempt failed, and the SpO2 dropped to 75%. The patient was reintubated and underwent conversion to surgical tracheostomy. Lastly, an 84-year-old man with hypertension and diabetes mellitus underwent PDT because of poor airway protection after spinal stenosis surgery. The 1st PDT attempt failed, and the SpO2 dropped to 79%. A SAD was inserted, and the subsequent 2nd attempt failed. This patient also underwent conversion to elective surgical tracheostomy.

**DISCUSSION**

In the present retrospective observational study, most patients (94.9%) underwent successful PDT without endotracheal guidance. Although four patients experienced hypoxia requiring reintubation or SADs during the procedure, there were no hypoxia-related sequelae.

The initially introduced standard PDT procedure included endotracheal guidance using bronchoscopy [15]. However, bronchoscopy requires an experienced and professional physician with additional assistants. Devices and equipment for PDT should also include a bronchoscope. To overcome the complexity and high degree of the required labor force, physicians have developed alternative endotracheal guides, such as ultrasound [10,11] and light sources [12]. Finally, PDT without endotracheal guidance has also been introduced [13,14].
Recently, PDT has been considered safe, but procedures requiring advanced airway management are often dangerous and devastating and may even lead to death. Common immediate or early complications occurring within 7 days are bleeding, hypoxia, posterior tracheal wall injury, tracheal tube obstruction, and so on. In the present study, one of the early complications was hypotension (16 patients, 20.5%), which is thought to be associated with sedative use. Hypoxia (4 patients, 5.1%) and bleeding (5 patients, 6.4%) were also reported. Hypotension and bleeding were minor events that resolved by conservative management. Major surgical problems, such as tracheal wall injury and tube obstruction, were not reported.

Although four patients required airway management because of hypoxia during PDT, normal range oxygenation was recovered after proper airway management without any hypoxia-related sequelae. However, conversions to surgical tracheostomy were required in two patients (2.6%). Beyond 7 days, late complications such as subglottic or tracheal stenosis, unplanned decannulation, stomal infection, and permanent voice changes can occur [16,17]. However, in this study, severe late complications in need of medical attention were not reported.

In the present study, remifentanil and midazolam were routinely used for procedural analgesia and sedation. Although hypoxia was observed in 5.1% of patients, apnea was not observed. Due to endotracheal intubation with or without mechanical ventilation, most patients were receiving an continuous remifentanil infusion titrated to minimize pain and agitation before PDT. As a result, patients received relatively high doses of remifentanil via continuous infusion and an additional bolus of midazolam for the PDT procedure without apnea event. The higher incidence of hypotension (20.5%) than hypoxia without any apnea event can be explained by the basal opioid exposure of the patients.

Previous studies on PDT without endotracheal guidance found that the procedure was relatively safe. However, Pattnaik et al. [14] reported several important complications in 300 cases of PDT without endotracheal guidance, including two cases (0.6%) of false lumen insertion, two cases (0.6%) of major bleeding requiring transfusion, and two cases (0.6%) of death within 24 hours as early complications. Additionally, four cases (1.3%) of subglottic stenosis were also reported as late complications. Jackson et al. [13] compared the outcomes of PDT with or without bronchoscopy guidance in trauma patients. There was no significant difference in the incidence of major early and late complications. One case of cardiac arrest was reported in the PDT with bronchoscopy guide group.

In this study, the patients received PDT without endoscopic guidance in the ICU. The use of endotracheal guides facilitates a safe and precise procedure [9-11], but this usually requires considerable technician labor, costs, and time. Furthermore, in many hospitals, bronchoscopy and real-time ultrasound are not always accessible for tracheostomy, and physicians must wait for the devices and technicians to be prepared. On the other hand, clinicians performing PDT without endotracheal guidance do not need to wait for devices or technicians, and the procedure can be performed immediately if the patient and operating physician are ready. The present investigation reports a lower incidence of major complications than previous studies.

The authors also tried to discriminate risk factors to predict PDT failure. Although previous studies have reported PDT

### Table 4. Characteristics of patients with PDT failure on the first attempt

<table>
<thead>
<tr>
<th>Age (yr)/sex</th>
<th>Underlying disease</th>
<th>Reason for MV</th>
<th>Duration from MV to PDT (day)</th>
<th>PDT course</th>
<th>Complications during PDT</th>
<th>Special note</th>
</tr>
</thead>
<tbody>
<tr>
<td>65/F</td>
<td>NSCLC (adenocarcinoma)</td>
<td>Pneumonia, atelectasis</td>
<td>15</td>
<td>1st attempt failure</td>
<td>Hypoxia (SpO₂, 67%)</td>
<td></td>
</tr>
<tr>
<td>59/M</td>
<td>Olivopontocerebellar atrophy</td>
<td>Postoperative care (gastric ulcer perforation)</td>
<td>19</td>
<td>1st attempt failure</td>
<td>Hypoxia (SpO₂, 76%)</td>
<td>Tracheostomy site obstruction, Heparinization for CRRT</td>
</tr>
<tr>
<td>48/F</td>
<td>Alcoholic liver cirrhosis</td>
<td>Postoperative care (liver transplantation)</td>
<td>23</td>
<td>1st attempt failure</td>
<td>Hypoxia (SpO₂, 75%)</td>
<td>Bloody secretion from E-tube, Thrombocytopenia (platelet count, 38,000/μl)</td>
</tr>
<tr>
<td>84/M</td>
<td>Hypertension, diabetes mellitus</td>
<td>Postoperative care (spinal stenosis)</td>
<td>20</td>
<td>1st attempt failure</td>
<td>Hypoxia (SpO₂, 79%)</td>
<td></td>
</tr>
</tbody>
</table>

PDT: percutaneous dilatational tracheostomy; MV: mechanical ventilation; NSCLC: non-small-cell lung carcinoma; CRRT: continuous renal replacement therapy; E-tube: endotracheal tube.
without endoscopic guidance to be safe, they have also reported fatal complications, such as false-lumen insertion, major bleeding, and cardiac arrest [13,14]. However, there are no available data on clinical factors associated with failure or fatal complications. In the presenting study, we also failed to discriminate the risk factors for the failure in the first PDT attempt.

The present investigation has several limitations. First, it was a retrospective observational study with a small number of patients in a single tertiary medical center. However, most patients were homogeneous; most were treated in the medical department, and PDT was performed by a single intensivist. Second, the study did not include patients who initially underwent surgical tracheostomy, suggesting selection bias. There is a possibility that those who underwent initial surgical tracheostomy exhibited a difficult anatomy for tracheostomy. Third, an experienced single medical intensivist performed PDT in the ICU. The physician had good performance in this study, but the proficiency of the operator was the key point in performing PDT without endotracheal guidance. Thus, there is the possibility that safety is not guaranteed in PDT depending on the physician’s ability.

In conclusion, PDT without endotracheal guidance can be performed safely on most ICU patients. Regarding the costs, time, and requirement of specific technicians for endotracheal guidance, PDT performed by experienced physicians using precise landmarks can be a feasible choice. Further studies comparing PDT with and without endotracheal guidance can yield precise clinical guidance.

**CONFLICT OF INTEREST**

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

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**AUTHOR CONTRIBUTIONS**

Conceptualization: DHL. Data curation: DHL. Formal analysis: JEK. Methodology: all authors. Project administration: all authors. Visualization: all authors. Writing–original draft: JEK. Writing–review and editing: all authors.

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INTRODUCTION

Septic shock is a life-threatening condition that is a major healthcare burden worldwide. The reported mortality from septic shock ranges from 42% to 53% [1-3]. To improve outcomes, early diagnosis, appropriate antibiotics, infectious source drainage, and rapid hemodynamic restoration should be provided. The serum lactate level has been added as a component parameter of the criteria used to diagnose septic shock, and it is also used to guide tissue perfusion restoration. Previously reported evidence suggested that the serum lactate level might be an independent factor associated with poor septic shock management outcomes.
Recently proposed diagnostic criteria (sepsis and septic shock [Sepsis-3]) recommend that septic shock be diagnosed if a patient has clinical features of sepsis with hypotension that requires vasopressors to maintain a mean arterial blood pressure (mABP) of 65 mm Hg or higher and has a serum lactate level of 2 mmol/L or more despite adequate volume resuscitation [4]. Using those criteria, in-hospital mortality is in excess of 40%. The decision to include lactate levels in the septic shock diagnostic criteria was based on a systematic review of 44 epidemiologic studies reporting septic shock outcomes. A previous study that influenced the decision to include serum lactate levels in the diagnostic criteria for septic shock reported an increase in the adjusted odds ratio [OR] for in-hospital mortality from 1.4 (95% confidence interval [CI], 1.35–1.45) to 3.03 (95% CI, 2.68–3.45) as the serum lactate level rose from 2 to 10 mmol/L [1]. Treatment involves initial fluid resuscitation and vasopressor administration to maintain adequate perfusion pressure, with additional treatment guided by frequent reassessments of hemodynamic status to achieve adequate tissue perfusion. Reassessments should include physical examinations, urine output, and serum lactate levels [5-7]. Previous studies reported an association between early lactate clearance and reduced in-hospital mortality among septic shock patients [8-10].

The serum lactate level, one of the most important markers in septic shock patients, depends on the lactate production and elimination rates. Increased serum lactate levels occur mainly in situations that cause increased lactate production such as shock, which causes anaerobic metabolism due to inadequate tissue perfusion (type A lactic acidosis). However, deterioration in lactate elimination can also cause increasing serum lactate (type B lactic acidosis), and that condition has been associated with malignancy and the use of specific medications [11-14]. The liver plays the major role in lactate elimination, so impaired liver function could decrease it [11]. Therefore, in septic shock patients with documented cirrhosis, impaired liver function might result in higher lactate levels, impaired lactate clearance, and delayed normalization of lactate during septic shock. There is currently a scarcity of information specific to differences in serum lactate levels and lactate clearance between cirrhotic and non-cirrhotic septic shock patients.

Therefore, the primary objective of this study was to identify differences in serum lactate levels and lactate clearance between cirrhotic and non-cirrhotic septic shock patients. The secondary objective was to evaluate the utility of lactate levels and lactate clearance in predicting in-hospital mortality among cirrhotic and non-cirrhotic septic shock patients.

**MATERIALS AND METHODS**

This study protocol was approved by the Institutional Review Board of Siriraj Hospital (IRB No. 421/2018). The requirement to obtain informed consent was waived due to our study’s retrospective design.

**Design and Study Population**

This retrospective cohort study was conducted at the medical intensive care unit of a referral, university-affiliated medical center. The study included adult patients (at least 18 years old) who were admitted between January 2012 and June 2018 and met the criteria for a septic shock diagnosis according to the Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012 [15]. Septic shock was defined as hypotension with an mABP lower than 65 mm Hg or requiring a vasopressor to maintain mABP ≥65 mm Hg and the presence of a documented infection with evidence of systemic inflammation. Patients with prolonged shock (longer than 24 hours), do-not-resuscitate orders, pregnancy, or a lack of serum lactate level data at baseline or follow-up were excluded. Every septic shock patient was resuscitated according to a septic shock protocol that includes fluid resuscitation, vasopressor therapy, antimicrobial initiation within 1 hour, appropriate source control, and organ support.

**KEY MESSAGES**

- The initial serum lactate level and serum lactate at 6 hours were significantly higher in cirrhotic septic shock patients than in non-cirrhotic septic shock patients. However, lactate clearance did not differ significantly between the groups.
- Cut-off values for initial lactate, lactate at 6 hours, and lactate clearance of >4 mmol/L, >2 mmol/L, and <10%, respectively, were identified as predictors of in-hospital mortality among non-cirrhosis patients.
- Among those with cirrhosis, the cut-off values predicting in-hospital mortality were >5 mmol/L, >5 mmol/L, and <20%, respectively.
- None of the three evaluated serum lactate parameters was found to be an independent predictor of in-hospital mortality in either study group.
Data Collection

We performed an electronic medical records review from which we collected and recorded patient baseline characteristics: age, sex, underlying conditions, severity score, and vital signs. The baseline serum lactate level was defined as the first serum lactate measurement from an arterial or venous blood sample [16] after the septic shock diagnosis. According to the septic shock diagnostic criteria used during the study period, serum lactate was measured within 3 hours after the septic shock diagnosis. To calculate serum lactate clearance, we used the following formula: [(initial serum lactate level–follow-up serum lactate)/initial serum lactate×100]. At our center, follow-up serum lactate measurements were performed after patients were resuscitated and achieved the macro-circulation goal of mABP ≥65 mm Hg, usually 6 hours after the initiation of resuscitation. Data specific to the amount of fluid resuscitation, vasopressor type and dosage, organ support requirements, and treatment outcomes were also recorded. Patients were classified into the cirrhosis septic shock group if they had been diagnosed with cirrhosis using evidence obtained from ultrasonography, computerized tomography, or magnetic resonance imaging before they developed septic shock. Patients without a previous diagnosis of cirrhosis were classified into the non-cirrhosis group. The primary outcome of this study was in-hospital mortality.

Statistical Analysis

Continuous data are expressed as the mean±standard deviation, and categorical data are expressed as percentages. Independent t-testing was used to compare continuous variables with a normal distribution. For the comparison of non-normally distributed continuous variables, the Mann-Whitney U-test was used. The chi-square test or Fisher’s exact test was used to compare categorical variables.

To identify predictive factors associated with in-hospital mortality, patients were classified into non-cirrhosis and cirrhosis groups. A comparative analysis was then performed between the survivors and non-survivors in each group. A receiver operating characteristic (ROC) curve analysis was performed to identify cut-off values for the continuous variables that differed significantly between the survivors and non-survivors in each group. Each optimal cut-off value, along with its sensitivity and specificity, was determined using Youden’s index [17]. The largest area under the ROC curve (AUC) was used to identify which variable (initial lactate, lactate at 6 hours, or lactate clearance) best predicted in-hospital mortality. Variables were reclassified into two groups using the ROC curve–identified cut-off values, and then univariate analyses were performed. Risk is expressed as an unadjusted OR with the 95% CI. Predictive factors with a P-value equal to or less than 0.1 and other factors of interest were enrolled in binary logistic regression analyses. The results of the multivariate analysis are shown as adjusted OR with the 95% CI and P-value. Independent predictive factors associated with in-hospital mortality are those with a P-value equal to or less than 0.05. All statistical analyses were performed using SPSS ver. 18 (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 777 septic shock patients were enrolled in this study. Of them, 91 patients (11.7%) had been diagnosed with cirrhosis by radiological imaging before they developed septic shock. The demographic and clinical characteristics of the study participants are shown in Table 1. The mean age of the patients was 63.8±16.4 years, and 50.6% of them were male. There was no significant difference in the baseline APACHE II score or mABP between the cirrhosis and non-cirrhosis patients. However, the cirrhotic septic shock patients had significantly higher body mass index, lower temperature, and slower heart rate than the non-cirrhosis patients. The most common infection in the non-cirrhosis patients was pneumonia (34.7%). Intra-abdominal infections were the most common infection among cirrhosis patients (39.6%).

Cirrhosis patients received a larger volume of fluid resuscitation during days 2 and 3 after septic shock than the non-cirrhosis patients. The maximum vasopressor dose did not differ between the groups, but the cirrhosis patients required adrenaline and dopamine in higher proportions. Twenty-eight-day mortality was significantly higher among patients with both sepsis and cirrhosis than among patients without cirrhosis (34.1% vs. 24.1%; P=0.05); however, in-hospital mortality did not differ significantly between the groups (36.3% vs. 30.1%; P=0.23) (Table 1).

Regarding serum lactate levels (90% of cases reported venous lactate levels), the initial serum lactate level (7.5±6.1 vs. 4.3±3.7 mmol/L; P<0.001) and serum lactate at 6 hours (4.5±4.1 vs. 3.2±3.0 mmol/L; P=0.01) were both significantly higher among patients with both septic shock and cirrhosis than among patients without cirrhosis. Lactate clearance, however, did not differ significantly between the cirrhosis and non-cirrhosis groups (27.3%±24.7% vs. 23.5%±21.5%; P=0.35).
### Table 1. Demographic and baseline characteristics of study participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All (n=777)</th>
<th>Non-cirrhosis (n=686)</th>
<th>Cirrhosis (n=91)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>63.8±16.4</td>
<td>64.0±16.0</td>
<td>62.8±11.9</td>
<td>0.51</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22.7±5.0</td>
<td>22.4±4.8</td>
<td>25.0±6.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Male (%)</td>
<td>50.6</td>
<td>49.7</td>
<td>57.1</td>
<td>0.22</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>21.6±7.3</td>
<td>21.5±7.2</td>
<td>22.3±7.7</td>
<td>0.34</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>37.8±1.4</td>
<td>37.8±1.4</td>
<td>37.4±1.3</td>
<td>0.02</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>108.4±25.0</td>
<td>109.7±24.7</td>
<td>98.7±24.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Respiratory rate (/min)</td>
<td>26.6±6.6</td>
<td>26.8±6.5</td>
<td>25.6±6.9</td>
<td>0.12</td>
</tr>
<tr>
<td>Mean arterial blood pressure (mm Hg)</td>
<td>59.0±11.8</td>
<td>58.9±11.6</td>
<td>59.9±13.6</td>
<td>0.46</td>
</tr>
<tr>
<td>Underlying disease (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>48.6</td>
<td>50.4</td>
<td>35.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>36.0</td>
<td>36.3</td>
<td>34.1</td>
<td>0.73</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>14.9</td>
<td>15.9</td>
<td>7.7</td>
<td>0.04</td>
</tr>
<tr>
<td>Stroke</td>
<td>11.1</td>
<td>12.2</td>
<td>2.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>17.0</td>
<td>16.9</td>
<td>17.6</td>
<td>0.88</td>
</tr>
<tr>
<td>Malignancy</td>
<td>22.7</td>
<td>22.7</td>
<td>22.0</td>
<td>1.00</td>
</tr>
<tr>
<td>Source of infection (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>32.7</td>
<td>34.7</td>
<td>17.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>24.6</td>
<td>25.8</td>
<td>15.4</td>
<td>0.04</td>
</tr>
<tr>
<td>Intra-abdominal infection</td>
<td>18.3</td>
<td>15.5</td>
<td>39.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Skin/soft tissue infection</td>
<td>8.6</td>
<td>8.7</td>
<td>7.7</td>
<td>0.85</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>19.4</td>
<td>18.2</td>
<td>28.6</td>
<td>0.02</td>
</tr>
<tr>
<td>Treatment received</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluid day 1 (ml)</td>
<td>5,401.2±2,036.5</td>
<td>5,375.1±2,042.5</td>
<td>5,597.4±1,991.3</td>
<td>0.33</td>
</tr>
<tr>
<td>Fluid day 2 (ml)</td>
<td>2,045.6±1,588.7</td>
<td>1,998.1±1,549.4</td>
<td>2,422.3±1,820.8</td>
<td>0.04</td>
</tr>
<tr>
<td>Fluid day 3 (ml)</td>
<td>1,548.5±1,527.7</td>
<td>1,504.5±1,501.2</td>
<td>1,877.4±1,685.5</td>
<td>0.05</td>
</tr>
<tr>
<td>Norepinephrine (%)</td>
<td>81.3</td>
<td>80.5</td>
<td>87.9</td>
<td>0.11</td>
</tr>
<tr>
<td>Adrenaline (%)</td>
<td>16.6</td>
<td>15.6</td>
<td>24.2</td>
<td>0.05</td>
</tr>
<tr>
<td>Dopamine (%)</td>
<td>28.3</td>
<td>26.2</td>
<td>44.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Dobutamine (%)</td>
<td>4.1</td>
<td>4.3</td>
<td>1.7</td>
<td>0.50</td>
</tr>
<tr>
<td>Maximum dose of vasopressor&lt;sup&gt;b&lt;/sup&gt; (µg/kg/min)</td>
<td>0.40±0.62</td>
<td>0.41±0.63</td>
<td>0.33±0.47</td>
<td>0.23</td>
</tr>
<tr>
<td>Renal replacement therapy (%)</td>
<td>14.9</td>
<td>14.3</td>
<td>19.8</td>
<td>0.16</td>
</tr>
<tr>
<td>Ventilatory support (%)</td>
<td>61.6</td>
<td>62.2</td>
<td>57.1</td>
<td>0.36</td>
</tr>
<tr>
<td>Initial serum lactate level (mmol/L)</td>
<td>4.7±4.2</td>
<td>4.3±3.7</td>
<td>7.5±6.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum lactate at 6 hours (mmol/L)</td>
<td>3.3±3.1</td>
<td>3.2±3.0</td>
<td>4.5±4.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Serum lactate clearance (%)</td>
<td>23.9±21.8</td>
<td>23.5±21.5</td>
<td>27.3±24.7</td>
<td>0.35</td>
</tr>
<tr>
<td>In-hospital mortality (%)</td>
<td>30.8</td>
<td>30.1</td>
<td>36.3</td>
<td>0.23</td>
</tr>
<tr>
<td>28-Day mortality (%)</td>
<td>25.3</td>
<td>24.1</td>
<td>34.1</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation unless otherwise indicated.

<sup>a</sup>APACHE: Acute Physiology and Chronic Health Evaluation.

<sup>b</sup>Ranges from 0 to 71, and a higher score indicates greater disease severity;

<sup>c</sup>Maximum vasopressor dose was calculated by summing the norepinephrine dose (µg/kg/min), adrenaline dose (µg/kg/min), dopamine dose (µg/kg/min/100), and dobutamine dose (µg/kg/min/100).
In the non-cirrhotic septic shock patients, initial serum lactate (5.6±5.1 vs. 3.8±2.8 mmol/L; P<0.001) and lactate at 6 hours (4.1±4.3 vs. 2.8±2.0 mmol/L; P<0.001) were significantly higher, and lactate clearance was significantly lower (20.0%±20.4% vs. 25.1%±21.8%; P=0.02) among patients who died in the hospital than in those who survived. In the cirrhotic septic shock patients, only the initial serum lactate level was significantly higher among non-survivors than among survivors (9.6±5.8 vs. 6.9±5.9 mmol/L; P=0.01) (Table 2).

When we considered the influence of age and lactate levels in subgroup analyses of patients aged 18 to <60 years old, 60 to <80 years old, and ≥80 years old, we found no significant differences in the initial serum lactate level, serum lactate at 6 hours, or lactate clearance between the non-cirrhosis and cirrhosis groups in any age group (Table 3). Patients who required renal replacement therapy (RRT) had a significantly higher initial serum lactate level (7.4±6.2 vs. 4.2±3.5 mmol/L; P<0.001) and serum lactate at 6 hours (5.5±5.4 vs. 2.9±2.2 mmol/L; P<0.001) than patients who did not require RRT, and lactate clearance was significantly lower among patients who required RRT. 

### Table 2. Serum lactate parameters of the non-cirrhosis and cirrhosis groups

<table>
<thead>
<tr>
<th>Laboratory parameter</th>
<th>Non-cirrhosis patient</th>
<th>Cirrhosis patient</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Survivor (n=490)</td>
<td>Non-survivor (n=206)</td>
<td>P-value</td>
</tr>
<tr>
<td>Initial serum lactate level (mmol/L)</td>
<td>3.8±2.8</td>
<td>5.6±5.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum lactate at 6 hours (mmol/L)</td>
<td>2.8±2.0</td>
<td>4.1±4.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum lactate clearance (%)</td>
<td>25.1±21.8</td>
<td>20.0±20.4</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation.

### Table 3. Lactate parameters according to specific subgroups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All (n=777)</th>
<th>Non-cirrhosis (n=686)</th>
<th>Cirrhosis (n=91)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group*</td>
<td>(n=133)</td>
<td>(n=127)</td>
<td>(n=6)</td>
<td></td>
</tr>
<tr>
<td>≥80 yr</td>
<td>Initial serum lactate level (mmol/L)</td>
<td>4.4±3.4</td>
<td>4.3±3.4</td>
<td>5.6±3.6</td>
</tr>
<tr>
<td></td>
<td>Serum lactate at 6 hours (mmol/L)</td>
<td>2.9±2.1</td>
<td>3.0±2.2</td>
<td>2.3±0.5</td>
</tr>
<tr>
<td></td>
<td>Serum lactate clearance (%)</td>
<td>24.8±22.4</td>
<td>24.3±22.0</td>
<td>34.1±32.1</td>
</tr>
<tr>
<td>60–79 yr</td>
<td>Initial serum lactate level (mmol/L)</td>
<td>4.6±3.6</td>
<td>4.3±3.3</td>
<td>6.4±4.5</td>
</tr>
<tr>
<td></td>
<td>Serum lactate at 6 hours (mmol/L)</td>
<td>3.3±2.4</td>
<td>3.2±2.3</td>
<td>4.6±3.4</td>
</tr>
<tr>
<td></td>
<td>Serum lactate clearance (%)</td>
<td>24.0±21.9</td>
<td>23.8±21.5</td>
<td>26.0±26.2</td>
</tr>
<tr>
<td>18–&lt;59 yr</td>
<td>Initial serum lactate level (mmol/L)</td>
<td>5.1±5.2</td>
<td>4.5±4.4</td>
<td>9.5±7.8</td>
</tr>
<tr>
<td></td>
<td>Serum lactate at 6 hours (mmol/L)</td>
<td>3.6±4.2</td>
<td>3.5±4.1</td>
<td>4.9±5.2</td>
</tr>
<tr>
<td></td>
<td>Serum lactate clearance (%)</td>
<td>22.8±21.2</td>
<td>22.3±21.1</td>
<td>27.4±21.9</td>
</tr>
<tr>
<td>Organ support</td>
<td>Renal replacement therapy*</td>
<td>(n=116)</td>
<td>(n=98)</td>
<td>(n=18)</td>
</tr>
<tr>
<td></td>
<td>Initial serum lactate level (mmol/L)</td>
<td>7.4±6.2</td>
<td>7.0±6.2</td>
<td>9.3±5.8</td>
</tr>
<tr>
<td></td>
<td>Serum lactate at 6 hours (mmol/L)</td>
<td>5.5±5.4</td>
<td>5.6±5.6</td>
<td>4.7±3.7</td>
</tr>
<tr>
<td></td>
<td>Serum lactate clearance (%)</td>
<td>18.5±19.1</td>
<td>18.8±19.4</td>
<td>16.3±16.4</td>
</tr>
<tr>
<td></td>
<td>No renal replacement therapy</td>
<td>(n=661)</td>
<td>(n=588)</td>
<td>(n=73)</td>
</tr>
<tr>
<td></td>
<td>Initial serum lactate level (mmol/L)</td>
<td>4.2±3.5</td>
<td>3.9±2.9</td>
<td>7.1±6.1</td>
</tr>
<tr>
<td></td>
<td>Serum lactate at 6 hours (mmol/L)</td>
<td>2.9±2.2</td>
<td>2.8±1.9</td>
<td>4.5±4.2</td>
</tr>
<tr>
<td></td>
<td>Serum lactate clearance (%)</td>
<td>24.9±22.1</td>
<td>24.4±21.8</td>
<td>29.7±25.7</td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation.

*The initial serum lactate level, serum lactate at 6 hours, and serum lactate clearance did not differ significantly across the three age groups; *The initial serum lactate level, serum lactate at 6 hours, and serum lactate clearance did differ significantly between patients who received and did not receive renal replacement therapy (P<0.001, P<0.001, and P=0.02, respectively).
who required RRT (18.5%±19.1% vs. 24.9%±22.1%; P=0.02) (Table 3).

To identify serum lactate and lactate clearance cut-off values that predict in-hospital survival, we used a ROC curve analysis. The AUC and optimal cut-off values (according to Youden’s index) for each lactate parameter are shown in Figure 1 and Supplementary Table 1. In non-cirrhotic septic shock patients, an initial serum lactate level of 4 mmol/L or more, a lactate level at 6 hours of 2 mmol/L or more, and lactate clearance of 10% or less predicted in-hospital mortality. In cirrhotic septic shock patients, an initial serum lactate level of 5 mmol/L or more, a lactate level at 6 hours of 5 mmol/L or more, and lactate clearance of 20% or less were identified as cut-off values, but they showed no association with in-hospital mortality.

Table 4 shows the independent predictive factors for in-hospital mortality among non-cirrhotic septic shock patients. Our multivariate analysis model included 17 mortality-associated parameters identified in the univariate analyses with a P-value <0.1. The multivariate analysis revealed that an APACHE II score ≥20, maximum vasopressor dose ≥0.2 µg/kg/min, pneumonia, bacteremia, requirement for RRT, and need for mechanical ventilator support were predictive factors associated with in-hospital mortality. That same analysis revealed that a body mass index ≥21 kg/m² and urinary tract infection were protective factors against in-hospital mortality.

In cirrhotic septic shock patients, 13 parameters were found to be significantly associated with in-hospital mortality in the univariate analyses. The multivariate model identified a maximum vasopressor dose ≥0.2 µg/kg/min and the need for mechanical ventilator support as independent predictive factors associated with in-hospital mortality (Table 5).

Because the relationships among the initial serum lactate level, serum lactate at 6 hours, and lactate clearance could interfere with the result of a multivariate analysis, we analyzed

**Figure 1.** Receiver operative characteristic (ROC) curve analysis to identify the serum lactate level cut-off value predicting in-hospital mortality. (A) ROC curve for non-cirrhosis patients. (B) ROC curve for cirrhosis patients. AUC: area under the curve; CI: confidence interval.
Tongyoo S, et al. Lactate level in cirrhosis with septic shock

Table 4. Univariate and multivariate analyses to identify variables independently associated with in-hospital mortality in non-cirrhosis patients

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Age ≥ 65 yr</td>
<td>1.33 (0.96–1.85)</td>
<td>0.09</td>
</tr>
<tr>
<td>Body mass index ≥21 kg/m²</td>
<td>0.63 (0.41–0.95)</td>
<td>0.03</td>
</tr>
<tr>
<td>APACHE II score ≥20</td>
<td>2.80 (1.94–4.04)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Temperature ≥37.5°C</td>
<td>0.62 (0.42–0.92)</td>
<td>0.02</td>
</tr>
<tr>
<td>Respiratory rate ≥25/min</td>
<td>1.50 (1.08–2.08)</td>
<td>0.02</td>
</tr>
<tr>
<td>Fluid day 1 ≥5,500 ml</td>
<td>1.34 (0.96–1.80)</td>
<td>0.06</td>
</tr>
<tr>
<td>Maximum vasopressor dose ≥0.2 (µg/kg/min)²</td>
<td>4.55 (3.21–6.45)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Initial serum lactate level ≥4 mmol/L</td>
<td>1.83 (1.32–2.55)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum lactate at 6 hours ≥2 mmol/L</td>
<td>2.62 (1.63–4.22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum lactate clearance ≥10%</td>
<td>0.63 (0.41–0.97)</td>
<td>0.04</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.36 (0.98–1.88)</td>
<td>0.07</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1.58 (1.03–2.41)</td>
<td>0.04</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2.33 (1.66–3.27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>0.40 (0.26–0.62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>1.68 (1.12–2.52)</td>
<td>0.01</td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td>4.77 (3.05–7.46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ventilatory support</td>
<td>13.11 (7.53–22.84)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Maximum vasopressor dose was calculated by summing the norepinephrine dose (µg/kg/min), adrenaline dose (µg/kg/min), dopamine dose (µg/kg/min/100), and dobutamine dose (µg/kg/min/100).

Table 5. Univariate and multivariate analyses to identify variables independently associated with in-hospital mortality in cirrhosis patients

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>APACHE II score ≥20</td>
<td>1.80 (0.74–4.39)</td>
<td>0.19</td>
</tr>
<tr>
<td>Temperature ≥37.0°C</td>
<td>0.57 (0.22–1.45)</td>
<td>0.23</td>
</tr>
<tr>
<td>Fluid day 1 ≥5,500 ml</td>
<td>3.50 (1.43–8.59)</td>
<td>0.08</td>
</tr>
<tr>
<td>Maximum vasopressor dose ≥0.2 (µg/kg/min)²</td>
<td>4.59 (1.84–11.45)</td>
<td>0.001</td>
</tr>
<tr>
<td>Initial serum lactate level ≥5 mmol/L</td>
<td>3.35 (1.30–8.64)</td>
<td>0.01</td>
</tr>
<tr>
<td>Serum lactate at 6 hours ≥5 mmol/L</td>
<td>4.2 (0.87–20.34)</td>
<td>0.06</td>
</tr>
<tr>
<td>Serum lactate clearance ≥20%</td>
<td>1.03 (0.23–4.58)</td>
<td>1.00</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>5.00 (0.41–27.41)</td>
<td>0.04</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>3.71 (1.22–11.61)</td>
<td>0.02</td>
</tr>
<tr>
<td>Receiving adrenaline</td>
<td>2.39 (1.00–5.73)</td>
<td>0.05</td>
</tr>
<tr>
<td>Receiving dopamine</td>
<td>6.07 (2.13–17.28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td>0.15 (0.02–1.37)</td>
<td>0.09</td>
</tr>
<tr>
<td>Ventilatory support</td>
<td>5.00 (1.11–22.44)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*Maximum vasopressor dose was calculated by summing the norepinephrine dose (µg/kg/min), adrenaline dose (µg/kg/min), dopamine dose (µg/kg/min/100), and dobutamine dose (µg/kg/min/100).

The data by entering those three lactate parameters one-by-one. Even so, we did not identify any of them as an independent predictive factor associated with in-hospital mortality in either the non-cirrhosis or cirrhosis groups.

DISCUSSION

The results of this study show that the initial lactate levels and lactate at 6 hours were both significantly higher among...
cirrhotic than non-cirrhotic septic shock patients. However, lactate clearance did not differ significantly between the groups. Twenty-eight–day mortality was significantly higher among cirrhosis patients, but in-hospital mortality did not differ significantly between the groups. For septic shock prognostic determination, baseline serum lactate was significantly higher among patients who died in the hospital than among those who survived in both the cirrhosis and non-cirrhosis groups. Our multivariate analyses revealed no independent association between any of the three lactate parameters we investigated and in-hospital mortality in either the cirrhotic or non-cirrhotic septic shock groups.

The elevation of lactate level in septic shock patients results from both an overproduction of lactate and decreasing lactate elimination. During shock, tissue hypoxemia occurs due to inadequate blood flow. That condition inhibits aerobic metabolism via Kreb's cycle, which results in the overproduction of lactate, the metabolic end product of anaerobic glycolysis. The liver is the major organ responsible for lactate elimination. Impaired liver function through either chronic or acute processes could result in delayed lactate clearance. In septic shock, liver dysfunction has been reported as a complication associated with poor outcomes. Therefore, the elevation of lactate from the combination of overproduction and under elimination might reflect the severity of septic shock. Among cirrhosis patients without sepsis, evidence of elevated lactate levels has been found in blood samples from both the hepatic vein and the femoral artery. Furthermore, the lactate level correlated directly with portal pressure and the severity of liver dysfunction. In patients with both septic shock and cirrhosis, a previous study reported that lactate clearance was delayed compared with lactate clearance in non-cirrhosis patients. However, those studies did not report the baseline serum lactate levels or the lactate levels 6 hours after resuscitation. Our study demonstrated that septic shock patients with underlying cirrhosis had significantly higher baseline serum lactate levels and significantly higher lactate 6 hours after septic shock resuscitation than non-cirrhotic septic shock patients. Given that the initial mABP did not differ significantly between the groups, the observed higher lactate levels in the cirrhotic septic shock patients could be associated with impaired liver clearance rather than lactate overproduction from tissue hypoxemia caused by shock. Given the higher adrenaline requirement we found among cirrhosis patients, another explanation for the higher serum lactate levels among cirrhosis patients could be overt aerobic glycolysis secondary to β-2 adrenergic receptor stimulation during adrenaline infusion. However, that might not be the major cause of the lactate difference because only 24.2% of the cirrhosis patients received adrenaline during septic shock resuscitation.

Information from the Surviving Sepsis Campaign database indicates that a lactate level greater than 4 mmol/L is an independent predictor of septic shock mortality. Other studies found that higher lactate levels were associated with higher septic shock mortality. The recently proposed Sepsis-3 definition, “lactate level greater than 2 mmol/L together with a requirement for vasopressor to maintain mABP in the absence of volume depletion,” was used in our study as the clinical criteria for diagnosing septic shock. Using that lower lactate level cut-off value improves the sensitivity for diagnosis; however, it might also limit the specificity in predicting a poor prognosis. Because it had the largest AUC, the initial serum lactate might be a better indicator than the lactate level at 6 hours or lactate clearance for predicting in-hospital mortality in both the cirrhosis and non-cirrhosis groups. Using the highest Youden's index value, an initial serum lactate level of greater than 4 mmol/L for non-cirrhosis patients and greater than 5 mmol/L for cirrhosis patients could be used as cut-off values for predicting in-hospital mortality among septic shock patients. Our multivariate analysis did not identify initial lactate, lactate at 6 hours, or lactate clearance as independent predictors of in-hospital mortality in either the cirrhotic or non-cirrhotic septic shock group. That might reflect the fact that we included multiple parameters that represent patient hemodynamic status and the severity of septic shock—baseline blood pressure, APACHE II score, day 1 fluid requirement, and maximum vasopressor dose—in our multivariate analysis model.

In contrast to previous studies that reported that lactate clearance was delayed among patients with both cirrhosis and septic shock compared with non-cirrhosis patients, the results of our study do not support that finding. Lactate clearance was actually higher in our cirrhotic septic shock patients than in our non-cirrhotic septic shock patients, but the difference between groups was not statistically significant. Furthermore, lactate clearance was not found to be a significant predictor of septic shock outcomes among cirrhosis and non-cirrhosis patients. The results of our subgroup analyses showed that both cirrhosis and non-cirrhosis patients who required RRT had significantly higher initial serum lactate levels and serum lactate at 6 hours than those who did not require RRT, and lactate clearance was significantly lower among patients who required RRT. Notably, cirrhosis patients...
who required RRT did not have significantly lower lactate clearance than non-cirrhosis patients who required RRT, and cirrhosis patients with no RRT did not have significantly higher lactate clearance than non-cirrhosis patients with no RRT. These findings suggest that preserved renal function plays an important role in lactate clearance among resuscitated septic shock patients, especially those with cirrhosis. Another possible explanation for the high lactate clearance observed among our cirrhosis patients was the higher fluid volume that they received during resuscitation because cirrhosis patients received slightly more fluid than non-cirrhosis patients. However, the difference in fluid resuscitation volume between groups on the 1st day of treatment was not significant.

Given the lack of association between liver function testing, including alanine transaminase, aspartate transaminase, alkaline phosphatase, and bilirubin levels, and the severity of liver disease, we decided to use a radiologically confirmed diagnosis of cirrhosis in this study. However, some asymptomatic cirrhosis patients who had no documented radiological imaging might have been allocated to the non-cirrhosis group. We did not use abnormal liver function tests to classify patients into the liver disease group because a certain proportion of non-cirrhosis sepsis patients can also have abnormal liver function tests [4].

We also observed that cirrhosis patients had a lower proportion of underlying hypertension, coronary artery disease, and stroke than the non-cirrhosis patients. The heart rates of cirrhosis patients were also significantly lower than in the non-cirrhosis group. Those findings could be explained by the hyperdynamic circulation associated with arterial vasodilatation, cirrhosis cardiomyopathy, and autonomic dysfunction. Arterial vasodilation is believed to be due to portosystemic shunting and bacterial translocation that produce redistribution of the blood volume, increased splanchnic blood flow, and decreased systemic vascular resistance [22]. The leading source of infection among cirrhosis patients was intra-abdominal infection, whereas it was pneumonia in non-cirrhosis patients. The higher proportion of intra-abdominal infection among cirrhosis patients has been reported by several studies [23,24]. Immune dysfunction combined with portosystemic shunting prevents gut-derived bacteria and their toxins from being cleared from portal circulation by the liver, which could be the main reason for an increased risk of infection among cirrhosis patients [25].

The limitations of this study should be mentioned. First, the diagnosis of cirrhosis using prior radiological imaging might have excluded patients with early cirrhosis, which could produce contamination bias. Considering that cirrhosis patients experience a range of severity from mild to severe dysfunction, the unavailability of data about baseline liver function before patients developed septic shock could be a related limitation of this study. Second, recent updates in the definition of septic shock might have produced discrepancies between the results of pre-definition-update study populations and current septic shock patients. Third, a certain proportion of patients could not achieve an mABP of 65 mm Hg or more 6 hours after the initiation of resuscitation. Thus, the lactate level reported at 6 hours that we used in our analyses might not reflect the restoration of microcirculation among those patients (and might explain our finding of no association between lactate clearance and septic shock outcomes in our study population). Fourth, the data from this study came from a single center that is also a national tertiary referral center that often receives complex cases that cannot be managed in a less sophisticated healthcare setting. As a result, the findings of this study might not be generalizable to other healthcare settings.

CONFLICT OF INTEREST

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

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AUTHOR CONTRIBUTIONS

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SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4266/acc.2021.00332.

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The effect of socioeconomic status, insurance status, and insurance coverage benefits on mortality in critically ill patients admitted to the intensive care unit

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Socioeconomic status is well known to be related to mortality [1] and is an important health issue in the management of the intensive care unit (ICU) in the United States and Europe [2]. Previous research also shows that the absence of health insurance is associated with a higher mortality rate among patients admitted to the ICU but unadjusted for the severity of illness and data from a single center [3]. Many observational studies have similarly suggested that a lack of insurance is associated with a higher mortality rate, and a systematic review from the American Thoracic Society found that critically ill patients without health insurance receive fewer critical care procedures and show poorer outcomes [3]. Lyon et al. [4] performed a retrospective cohort study using Pennsylvania hospital discharge data, analyzing a total of 138,720 critically ill adults <64 years of age treated at 167 acute care hospitals. These authors found that the absence of health insurance is associated with a significant increase in 30-day mortality and a decrease in the use of critical care procedures, such as tracheostomy, among critically ill patients using a detailed clinical risk-adjustment protocol. Their study also showed that use of a large multicenter dataset and detailed severity adjustment contributes to the analysis of health outcomes of uninsured critically ill patients [4].

In Europe, two different health care systems exist, specifically the tax-based health care system (THS) and the social health insurance system (SHI). Wernly et al. [5] performed a retrospective post-hoc analysis of data from 16 European countries, analyzing critically ill patients >80 years of age admitted to the ICU. They evaluated 4,941 patients with THS and 2,876 with SHI from the previous Very elderly Intensive Patient (VIP)1 and VIP2 studies [5] and found that the associated 30-day mortality rate was similar between both systems; however, patients with SHI were older, sicker, and frailer at baseline. They interpreted their findings as being indicative that a liberal admission policy and an increase in treatment limitations resulted in a trend of ICU excess mortality among patients with SHI [5].

In South Korea, Oh et al. [6] conducted a retrospective observational study of adults aged >20 years admitted to the ICU. They included 6,008 patients and found that socioeconomic status was not associated with 30-day mortality in the Korean National Health Insurance (NHI) coverage system. However, the occupation of the patient was associated with 1-year mortality [6]. Meanwhile, although the expansion of Medicaid services for low-income patients has improved mortality in the United States [7], the mortality rate is still higher among critically ill patients with public health insurance coverage only compared to those with ad-
Insurance benefits and ICU mortality

A financial burden is one of the biggest and most common stress factors among ICU survivors [9]. This burden also impacts their caregivers and is a serious problem. The absence of health insurance coverage is associated with increased mortality among ICU survivors, and a comprehensive approach is required to improve financial coverage for ICU survivors. In a Korean single tertiary hospital cohort study, Cha et al. [10] investigated discharged ICU survivors from 2012 to 2016 and found that low economic status was associated with a higher 1-year mortality rate, even among those patients supported by the NHI coverage system. This study also suggested the necessity of a comprehensive approach to national and regional health care policy for critically ill patients in the ICU and the discharged patients from ICU (ICU survivor) with low income or without insurance coverage [10].

In Yoo et al.'s study [11], the authors performed a single tertiary hospital cohort study that enrolled a total of 515 patients admitted to ICU over 5 years and showed that patients with NHI and additional benefit items experienced greater use of medical resources and improved in-hospital survival. Patients with the three benefit items “cancer,” “tuberculosis,” and “disability” had lower out-of-pocket medical expenditures due to the implementation of this policy but a higher in-hospital mortality rate [11]. These authors concluded that the Korean NHI benefit extension policy was associated with reduced in-hospital mortality of NHI beneficiaries requiring ventilator care, although the limited nature of a single-center retrospective cohort study requires that ICU care policies be derived from future, larger studies relying on a multicenter database or a big data analysis using Health Insurance Review and Assessment Service or NHI service data.

In conclusion, socioeconomic status, insurance status, and insurance coverage can have beneficial effects on mortality among critically ill patients admitted to the ICU. The national and regional health care support system is needed with balance between financial burden and management and supportive or end of life care for the critically ill patients and ICU survivors with low income or no insurance coverage.

CONFLICT OF INTEREST

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

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REFERENCES

Successful noninvasive ventilation in a severely acidic and hypercapnic comatose COVID-19 patient with multiple comorbidities: a case report

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Effective use of noninvasive ventilation in patients with chronic obstructive pulmonary disease is well-known. However, noninvasive ventilation in patients presenting with altered sensorium and severe acidosis (pH < 7.1) has been rarely described. Invasive mechanical ventilation is associated with high mortality in coronavirus disease 2019 (COVID-19), and use of noninvasive ventilation over invasive ventilation is an area of investigation. We report a case of COVID-19-induced acute exacerbation of chronic obstructive pulmonary disease in a 66-year-old male. His past medical history included obstructive sleep apnea, hypertension, cor pulmonale, atrial fibrillation, and amiodarone-induced hypothyroidism. On presentation, he had acute hypercapnic respiratory failure, severe acidosis (partial pressure of carbon dioxide [PCO₂], 147 mm Hg; pH, 7.06), and altered mentation. The patient was successfully managed with noninvasive ventilation, avoiding endotracheal intubation, invasive ventilation, and related complications. Although precarious, a trial of noninvasive ventilation can be considered in COVID-19-induced acute exacerbation of chronic obstructive pulmonary disease with hypercapnic respiratory failure, severe acidosis, and altered mentation.

Key Words: case report; chronic obstructive pulmonary disease; coma; COVID-19; noninvasive ventilation

Noninvasive ventilation (NIV) is beneficial as a first-line intervention in patients with acute hypercapnic respiratory failure (AHRF) secondary to acute exacerbation of chronic obstructive pulmonary disease (AECOPD). NIV is likely to reduce endotracheal intubation (ETI), intensive care unit (ICU) admission, morbidity, and mortality [1]. Altered consciousness, especially if severely depressed the need for immediate ETI and is considered a contraindication to use of NIV as it can predispose a patient to aspiration [2]. Although an association between the level of consciousness with NIV failure or in-hospital mortality in patients with acute hypoxic respiratory failure has not been found [3], severe acidosis (pH < 7.2) predicted prolonged NIV in severe AECOPD [4]. Despite the advantages of NIV, and even though its proper use has shown rapid clinical improvement in patients, some clinicians question the choice of NIV over invasive mechanical ventilation (IMV). For example, some reports predict failure of NIV at pH < 7.25, and NIV is not widely used as a first-line modality of ventilation in such conditions [4,5]. We report a case of hypercapnic coma with severe respiratory aci-
dosis in a patient with coronavirus disease 2019 (COVID-19)-induced AECOPD in which NIV was successfully used as first-line respiratory therapy.

CASE REPORT

Informed consent for publication was obtained from the patient. In our institute, ethical approval is not required for case reports. A 66-year-old male with no history of fever or travel was admitted to an outside institution with dyspnea and occasional cough. He tested positive for COVID-19 and was referred to our hospital. His past medical history included past smoker (80 pack-years), obstructive sleep apnea (OSA) for 40 years, and COPD for 10 years. He had been on home NIV, metered dose inhaler, and oxygen therapy for the previous 6 years. He also had suffered hypertension, cor-pulmonale, atrial fibrillation on amiodarone, and amiodarone-induced hypothyroidism for the previous 2 years. On arrival to the emergency department, he was conscious, tachypneic, and hemodynamically stable but desaturated. His oxygen saturation as measured by pulse oximetry (SpO₂) improved to 94% on oxygen via a simple facemask at 10 L/min. Although the patient’s oxygen saturation level was maintained throughout the evening, he became drowsy (Glasgow coma scale [GCS] E2V3M4) in the night due to carbon dioxide retention (arterial blood gas [ABG]: partial pressure of carbon dioxide [PCO₂], 134 mm Hg; pH, 7.0). Therefore, he was transferred to the COVID-19 ICU and immediately put on NIV. Electrocardiogram showed new-onset premature ventricular contractions. ABG reports immediately after initiating NIV, at 6 hours, and off NIV are shown in Figure 1B. Chest X-ray revealed mild COVID-19-related changes. After NIV for 24 hours, the patient’s sensorium (GCS E4V5M6) and overall clinical condition improved. He was shifted to oxygen via face mask at 6 L/min, which was later reduced to oxygen via nasal prongs at 4 L/min with SpO₂ 97%. However, considering his history of home NIV and OSA, NIV support was continued at night. He was afebrile throughout. Laboratory

![Figure 1(A) Mild ground-glass opacities left>right lung field with chronic obstructive pulmonary disease-related changes. (B) The arterial blood gas (ABG) parameters and (C) vital signs over time. NIV: noninvasive ventilation; PCO₂: partial pressure of carbon dioxide; PO₂: arterial partial pressure of oxygen; SaO₂: peripheral oxygen saturation; HCO₃⁻: bicarbonate; ED: emergency department; ICU: intensive care unit; HR: heart rate; RR: respiratory rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; SpO₂: oxygen saturation as measured by pulse oximetry.](image-url)

<table>
<thead>
<tr>
<th>ABG parameter</th>
<th>Immediately after NIV</th>
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<th>Off-NIV</th>
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<tr>
<td>pH</td>
<td>7.06</td>
<td>7.14</td>
<td>7.38</td>
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<tr>
<td>PCO₂ (mm Hg)</td>
<td>147</td>
<td>121</td>
<td>90.2</td>
</tr>
<tr>
<td>PO₂ (mm Hg)</td>
<td>152</td>
<td>402</td>
<td>169.5</td>
</tr>
<tr>
<td>SaO₂ (%)</td>
<td>98.5</td>
<td>99.6</td>
<td>99.8</td>
</tr>
<tr>
<td>HCO₃⁻ (mEq/L)</td>
<td>27.6</td>
<td>29.7</td>
<td>53.5</td>
</tr>
</tbody>
</table>
evaluations revealed a total leucocyte count within 4 hours of admission at 7,900/dl, and C-reactive protein on day 2 of admission was 88 mg/L. The patient was treated conservatively with the following empirical broad-spectrum antibiotics and medications: piperacillin/tazobactam 4.5 g intravenous injection, azithromycin 500 mg oral tablet, hydroxychloroquine 400 mg oral tablet twice on the first day and 200 mg twice a day for four days, dexamethasone 6 mg once per day, multivitamins, vitamin C, zinc, and one low-molecular-weight heparin 0.6 ml subcutaneous injection. The following cardiovascular medications were administered: amiodarone, metoprolol, amlodipine, and torsemide. Finally, the following respiratory medications were administered: metered dose inhaler tiotropium two puffs (9 µg each) OD, N-acetyl cysteine oral tablet, and oral doxofylline along with other supportive measures. After admission to the ICU, he remained afebrile, and his vital signs remained stable (Figure 1). His COVID-19 reverse transcription-polymerase chain reaction report returned negative, and he was discharged to the COVID-19 ward in stable condition on the fourth hospital day. The patient was subsequently discharged home on his chronic medication and home-NIV at night.

DISCUSSION

In the present case, NIV helped avoid ETI and its associated complications. A significant number of clinicians do not initiate treatment with NIV for fear of increased morbidity due to contraindications of NIV use, inexperience, unavailability of NIV, etc. [6]. In our case, the patient’s routine use of NIV at home during the night bolstered our decision to initiate NIV. In our opinion, carbon dioxide retention led to narcosis and altered consciousness, and improvement of the clinical condition and ABG can be attributed almost entirely to early use of NIV in the critical care unit. High-flow nasal cannula was not used in this case because it is primarily intended for improving oxygenation, and its superiority over NIV in managing AHRF is not established [7].

NIV achieves the same physiological response and rapid gas exchange as conventional mechanical ventilation [8,9]. Improvement in gas exchange, as evidenced by a reduction in the PCO₂ in the blood and improvement in pH within a few hours of starting NIV, predicts success in patients who are cooperative and tolerant of the NIV interface and have control over their airway secretions [10]. Moreover, the time, resources, and expertise required to initiate NIV are relatively less than those for performing IMV.

The literature indicates that COPD acts as a risk factor for severe COVID-19 and associated mortality [11]. Although coronaviruses can cause AECOPD, whether COVID-19 can precipitate AECOPD or not is under investigation [12]. However, acute exacerbation, which is defined as acute changes in symptoms needing a change in treatment, is often a clinical diagnosis [13]. Before his infection with COVID-19, the patient in the present case was stable on medications and home NIV, and the AECOPD leading to AHRF was precipitated by COVID-19 infection. Despite limited evidence of NIV use in patients with blood pH <7.25 and GCS 9/15, our patient did well. Close monitoring in the ICU was a crucial part of our management that allowed deference of IMV and its related complications. Nevertheless, the benefits of NIV over ETI and IMV should be weighed in each patient. When deciding whether to start NIV and continue the same for 24 hours, we considered certain factors, such as patient history and initial clinical condition, our ICU setup, and the team’s ability to continuously monitor the patient and intervene both immediately and rapidly in case of clinical deterioration. These considerations allowed us to successfully use NIV as first-line therapy in a hypercapnic, comatose, and severely acidic AECOPD patient with multiple comorbidities and COVID-19 infection in whom ETI and IMV would have been performed otherwise. Recently, the use of NIV in altered consciousness is gaining acceptability [3,14], and our case supports the effectiveness of NIV even in COVID-19-induced AECOPD.

With appropriate patient selection that is guided by detailed history, physical examination, and proper investigations, NIV can successfully be used in comatose AHRF caused by AECOPD.

CONFLICT OF INTEREST

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

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Dear Editor:

During the coronavirus disease 2019 (COVID-19) pandemic, expanding data on the presence of neurological complications has increased the interest in neurological involvement of COVID-19 and its possible pathophysiological mechanisms. Recently, many studies have been published showing that COVID-19 may cause neurological disorders [1-3]. The incidence of neurological disorders has been reported higher in severe patients requiring intensive care admission [2]. In COVID-19 patients, timely recognition and intervention of neurological disorders is crucial to improve outcomes. For this reason, we aimed to share the characteristics of neurological diseases in critically-ill COVID-19 patients who were admitted to our COVID-intensive care unit (ICU) between March 21, 2020 and March 21, 2021 for 1-year period.

In our ICU, 16 (4.9%) of 328 critically ill confirmed COVID-19 patients manifested with severe neurological diseases. Neurological findings were present in half of the patients at hospital admission and in the remaining eight patients, neurological problems were detected after ICU admission, in five of them after failure of awakening from cessation of sedation and in three of them after development of hemiparesis. Patients’ characteristics are shown in Table 1. There were 13 cases (81.3%) with ischemic stroke (IS), 10 of these patients had no previous history of IS. There was one case with Guillain-Barre syndrome, one with intracranial hemorrhage, and one with meningitis. IS was the most common neurological disease in our registry similar to other studies. However, when the risk factors of 13 patients regarding IS were evaluated, there was only one patient who did not have any risk factors for IS. Other patients had at least one risk factor for IS. There was hypertension in six patients, diabetes mellitus in five patients, cardiac disease in four patients, cerebrovascular disease in three patients and a long-term intensive care stay with renal failure and septic shock in one patient. Overall mortality was 37.5% in patients with neurological disease, whereas the 1-year mortality was 32.3% in our COVID-19 cohort.

The fact that detailed neurological evaluation could not be performed during a pandemic in the context of ICU, indicates that the incidence of neurological diseases might even be more than that reported, increasing morbidity and mortality. Patients can present with neurological complications before development of respiratory symptoms and signs during the COVID-19 course. Suspicion threshold for neurological complications should be low in cases of encephalopathy even if focal neurological deficits were not detected in COVID-19
Table 1. Patient characteristics of COVID-19 patients with neurological diseases

<table>
<thead>
<tr>
<th>Variable</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
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<th>P11</th>
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<td>71</td>
<td>54</td>
<td>55</td>
<td>19</td>
<td>51</td>
<td>82</td>
<td>22</td>
<td>57</td>
<td>82</td>
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<td>61 (52–73)</td>
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<td>M</td>
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<td>M</td>
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<td>M</td>
<td>NA</td>
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<td>Renal transplant</td>
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<td>HT, DM</td>
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<td>HT, DM</td>
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<td>HT, DM, CAD</td>
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<td>Malignancy</td>
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<td>6</td>
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<td>6</td>
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<td>7</td>
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<td>3</td>
<td>2</td>
<td>5</td>
<td>6</td>
<td>3</td>
<td>4</td>
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<td>15</td>
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<td>10</td>
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<td>15</td>
<td>15</td>
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<td>15</td>
<td>10</td>
<td>10</td>
<td>1.5 (11–19)</td>
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<td>1</td>
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<td>1.5 (0–3)</td>
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<td>7</td>
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<td>7</td>
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<td>3 (2–5.5)</td>
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<td>15</td>
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<td>3</td>
<td>8</td>
<td>87</td>
<td>7</td>
<td>2</td>
<td>10</td>
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<td>7</td>
<td>15</td>
<td>25</td>
<td>96</td>
<td>34</td>
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<tr>
<td>Length of stay in hospital (day)</td>
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<td>8</td>
<td>87</td>
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<td>6</td>
<td>16</td>
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<td>18</td>
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<td>25</td>
<td>96</td>
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<td>46</td>
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<td>8</td>
<td>21.5 (9.3–45.8)</td>
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<td>No</td>
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<td>No</td>
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<tr>
<td>Hospital mortality</td>
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<td>No</td>
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<td>No</td>
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</table>

patients. Although many studies have been published to reveal the relationship between COVID-19 and stroke, the majority of patients with IS during COVID-19 have advanced age and co-morbidities similar to our patients [4,5]. In a study of a high-volume center examining the relationship between COVID-19 and stroke, usual causes of stroke were found in most of the stroke cases. Moreover, all patients with an acute stroke without a usual etiology presented a severe infection requiring mechanical ventilation [5]. We believe that detailed etiological evaluations will give more accurate results in terms of determining COVID-19 related neurological complications. Therefore, more studies are needed to define the real incidence of neurological complications of COVID-19 and to clarify the underlying mechanism and causality between COVID-19 and neurological diseases.

CONFLICT OF INTEREST

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

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Dear Editor:

Hypoxemic respiratory insufficiency resulting from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection might not be due to a “typical” acute respiratory distress syndrome (ARDS) [1]. As pulmonary compliance appears relatively preserved during the early stages of coronavirus disease 2019 (COVID-19), a role for right-to-left shunting due to pulmonary vasoplegia has been hypothesized, suggesting a possible therapeutic benefit from inhaled pulmonary vasodilators [1] including milrinone, nitric oxide, and cyclic prostaglandins (e.g., iloprost). Inhaled iloprost improves oxygenation in non–COVID-19 ARDS with minimal adverse effects, and has mitigating effects on microvascular thrombosis, endothelial injury, and pulmonary inflammation [2] in animal models of ARDS, suggesting potential beneficial effects on mechanisms behind lung injury in COVID-19 [3]. We introduced inhaled iloprost as a rescue therapy for patients with refractory hypoxemia due to COVID-19. Systemic and pulmonary hemodynamics were monitored using a pulmonary artery catheter (PAC).

The local Institutional Review Board approved this study (IRB No. 2021_071). Informed consent for the treatment was obtained. We present retrospective data from a single center (December 2020–May 2021). We hypothesized that inhaled iloprost improves oxygenation by causing preferential pulmonary vasodilatation, which decreases the shunt fraction. We included data from mechanically ventilated patients with COVID-19, severe ARDS according to the Berlin criteria, and oxygenation index \( OI = (\text{mean airway pressure} \times \text{FiO}_2)/(\text{PaO}_2 \text{resures in mm Hg}) \) > 15 despite prone positioning, who were treated with iloprost, and in whom a PAC had been placed.

Iloprost (with a dose ranging 5–20 µg) was nebulized over 30 minutes and administered every 4 hours. The starting dose was 5 or 10 µg, which was increased on the basis of its clinical effects, up to a maximum of 20 µg. The effects on oxygenation were evaluated with arterial and mixed venous blood gas analyses. Samples were collected immediately before iloprost administration and then again at 30 and 60 minutes, and were repeated after any dose change. We calculated the right-to-left shunt fraction as follows:

\[
\frac{Q_s}{Q_t} = 100\% \times \frac{1 - CaO_2}{1 - CvO_2}
\]

where \( Q_s/Qt \) is the shunt fraction (percentage of cardiac output), and \( CaO_2 \) and \( CvO_2 \) are the arterial and mixed venous oxygen content, respectively.

Inhaled iloprost can improve oxygenation and shunt fraction in severe COVID-19

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Data are provided as median and interquartile range (IQR) or mean and standard deviation, and were compared using a paired t-test or Wilcoxon’s test, as appropriate (significance threshold, P<0.05).

In total, eight patients met the inclusion criteria. Their median age was 72.5 years (IQR, 67.3–73.8 years); six patients were male. The median positive end-expiratory pressure was 12 cm H2O (IQR, 10–16 cm H2O); the median OI was 17.8 (IQR, 14.9–20.7), and the median PaO2 to FiO2 (P/F) ratio was 75.8 (IQR, 69.6–97.0). Iloprost was started at a median of 23 days (IQR, 14–29.5 days) after onset of symptoms and 12 days (IQR, 9–20 days) after intubation. Up to three measurement sets were performed per patient, resulting in a total of 18 (Table 1). When only the first set of measurements were considered for each patient (n = 8), the median P/F ratio increased from 75.8 to 96.0 mm Hg (IQR, 69.6–97.0 vs. 78.4–144.4; P=0.012), the mean OI decreased from 17.3 to 14.4 (P=0.007; absolute and relative changes are shown in Figure 1A), and the mean Qs/Qt decreased from 43.6% to 37.5% (P=0.025) (Figure 1B). Considering all sets of measurements, the median P/F ratio increased from 93.5 to 105.0 mm Hg (IQR, 69.9–118.5 vs. 78.9–148.8; P<0.001), the mean OI decreased from 16.3 to 13.8 (P<0.001) (Supplementary Figure 1A), and the Qs/Qt decreased from 44.2% to 36.9% (P=0.001) (Supplementary Figure 1B). The relationships between changes in Qs/Qt and OI are shown in Figure 2. Two patients developed transient hemodynamic side effects: one patient had a drop in systemic vascular resistance, while the other experienced a decrease in left ventricular preload, evidenced by decreased capillary wedge pressure.

Our findings provide proof-of-concept that inhaled iloprost can improve oxygenation by decreasing the shunt fraction in mechanically ventilated patients with severe COVID-19 ARDS. To our knowledge, the effects of inhaled iloprost on shunt fraction in severe COVID-19 have not been previously described. These effects of iloprost on oxygenation reflect those described by Sonti et al. [4] after administration of inhaled epoprostenol. However, shunt fraction was not reported, and Tsareva’s study [5] included measurements at widely varying intervals. Tsareva et al. [5] found improved oxygenation after 5 days of treatment with iloprost, suggesting a possible disease-modifying effect. However, their patients were not critically ill, and shunt fraction was not described.

Interestingly, right-to-left shunt fraction at baseline varied widely (19%–70%), possibly reflecting different disease phenotypes in COVID-19. Furthermore, although most patients showed improved oxygenation after administration of iloprost, some had only a relatively shortlived response, advocating the use of more frequent or continuous nebulization.

We used inhaled iloprost exclusively as a rescue therapy in patients in whom other interventions failed, which might have led us to include only the sickest patients. In such patients, consolidative and even fibrotic changes might have shown predominance over the vasculopathy that is thought to dominate hypoxemia in early COVID-19 (i.e., our patients might have already been in the H-stage, as proposed byGattinoni et al. [1], wherein progressive parenchymal damage results in low compliance and a lesser role of vasoplegia).

From a pathophysiologic point of view, inhaled pulmonary vasodilators should have maximum effect during the L-stage, in which hypoxemia is thought to result primarily from ventilation/perfusion mismatch. Iloprost might have disease-modifying effects, by mediating platelet activation, endothelial damage, and pulmonary inflammation.

The retrospective nature of our study, its relatively small sample size, and the heterogenous patient population that

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dose (μg)</th>
<th>Measurement</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5, 10</td>
<td>2</td>
<td>First dose (10 μg) given before placement of PAC because of acute and severe hypoxaemia; measurement performed around second dose (20 μg)</td>
</tr>
<tr>
<td>2</td>
<td>10, 20</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>3</td>
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</tr>
<tr>
<td>4</td>
<td>10</td>
<td>3</td>
<td>This patient had been in prone position for 13 days and desaturated upon multiple trials supine positioning. To allow for supine positioning, we started iloprost despite an initial OI of up to 10.</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>2</td>
<td>Initial dose of 20 μg because of acute and severe hypoxaemia</td>
</tr>
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<td>6</td>
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<td>8</td>
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PAC: pulmonary artery catheter; OI: oxygenation index.
Inhaled iloprost for severe COVID-19

Figure 1. (A) The left panel depicts absolute changes in oxygenation index (OI), and the right panel shows relative changes in OI after iloprost administration in eight patients with severe coronavirus disease 2019 (COVID-19). A similar figure, including all measurements obtained, is presented in Supplementary Figure 1A. (B) The left panel depicts absolute changes and the right panel shows relative changes in shunt fraction (Qs/Qt) after iloprost administration in eight patients with severe COVID-19. A similar figure that includes all measurements obtained is shown in Supplementary Figure 1B. (A, B) Only measurements obtained around the first dose of iloprost received by each patient were included. The X axis shows the timepoints at which measurements were performed.

received unequal doses in different phases of the disease preclude us from drawing conclusions about the magnitude of the effects of iloprost.

Future studies should aim to determine the category of COVID-19 patients that responds best to inhaled pulmonary vasodilators. In addition, measuring pulmonary hemodynamic parameters might contribute to further understanding of COVID-19 pathophysiology.

In conclusion, we found that inhaled iloprost can improve oxygenation in severe COVID-19 by decreasing shunt fraction.
At baseline, shunt fraction varied widely, suggesting the existence of different mechanisms behind hypoxemia in severe COVID-19. Measuring the Qs/Qt should improve our understanding of refractory hypoxemia induced by SARS-CoV-2 and help tailor therapy for individual patients.

CONFLICT OF INTEREST

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

ACKNOWLEDGMENTS

We are grateful to our intensive care unit nurses, physicians and other staff. Without their help and expertise, the present study would not have been possible. We are specifically grateful for the contributions of Dr. O. Thomas in drafting the treatment protocol.

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Dear Editor:
A group of Tunisian investigators recently explored whether the early application of prone positioning can improve severe hypoxemia and respiratory failure in coronavirus disease 2019 (COVID-19) patients with spontaneous breathing—through a prospective observational study of patients admitted to the intensive care unit (ICU). After studying 21 subject-patients and 17 control-patients, who underwent prone positioning within 6 hours following ICU admission, they reported affirmatively in *Acute and Critical Care* [1] that yes, early prone positioning can improve severe hypoxemia—and significantly so.

But there was still a problem. The resolution of hypoxemia resulted in no change in the rate of mortality, or in the need for mechanical ventilation. How can that be possible? If ventilation/perfusion ratios are improving significantly throughout the lungs, and measured respiratory parameters are improving, why are patients still dying at the same rate? The answer may lie not in the lungs, but elsewhere. The Tunisian Investigators, in designing this study, made use of gravitational considerations within the lungs. In prone positioning, the beneficial changes in ventilation/perfusion ratios are based largely on gravity. But no one made use of gravitational considerations within the brain—even as concurrent reports [2,3] from 2021 have suggested their importance.

In the article, “Impact of prone position on outcomes of COVID-19 patients with spontaneous breathing” [1] all of 21 subject-patients were placed in prone position for 2 to 4 hours (as tolerated by the patient) followed by 2 hours of supine positioning during the day, and placed in prone position at night, when possible. “Gravitational ischemia in the brain” results from the mass effect of one part of the brain upon another in a gravitational field [2,3]. In any given head position, the top half of the brain (farthest from the center of the earth) is sitting on the bottom half as a weight-burden. In healthy individuals, head and body positions are roughly vertical for 16 hours a day, and then roughly horizontal for 8 hours at night during sleep. Ischemia, which may form on the bottom layers, is reversible in its early stages [2,3].

Gravitational ischemia in the brain may potentially be largely preventable by frequently changing the head tilt—just as ischemic skin breakdown, bed sores, and decubitus ulcers are currently prevented by frequent changes in general body positioning, focused on the effects of gravity. It might have been reasonably hoped that alternating between supine and prone positioning “rotisserie-style” would significantly relieve gravitational ischemia in the brain; but research results, like those of the Tunisian Investigators, suggest that this may not always
happen—at least not in brainstem vital centers.

Part of the answer to this apparent discrepancy may be revealed by a group of British investigators who recently reported [4] that “positional brain shift,” the sagging of the brain under the effect of gravity, is significant, relative to the specific geometric coordinates generated by magnetic resonance imaging (MRI) for the purpose of guiding stereotactic surgery. If the guiding coordinates are generated by an MRI done in supine position, the brain will move slightly away from those coordinates, if the patient is placed into a different position for surgery. This was confirmed by studying 11 health young adult volunteers, who were specifically moved from supine position to prone, and back again [4]. The head and body rotation studied by the British investigators was essentially identical to that utilized by the Tunisian investigators in their study.

The British investigators concluded that slight non-uniform brain shifting due to differences in head orientation can lead to a significant discrepancy between the planned and the actual location of surgical targets [4]. Additionally, strain analysis in their study revealed local variations in compressibility within the brain. When horizontally rotating from prone position back to supine, the anterior regions showed expansion (with changes in both volume and shape), and the posterior regions showed compression, mostly dominated by changes in shape [4].

Given its low stiffness, brain tissue shifts occur within the cranial vault under the influence of gravity, due to changes in head orientation even in normal healthy individuals without any surgical intervention [4]. The British investigators thus found that in repositioning young healthy adults from prone position to supine, the posterior fossa is compressed. This movement has a potential to compress brainstem autonomic nuclei, predisposing to ischemia formation there.

Data from the Tunisian investigators [1] and the British investigators [4], taken together, suggests that upright head position (or at least partially upright) may be required to relieve gravitational ischemia in the brainstem autonomic nuclei. Intermittently elevating the patient’s head by 30° may be helpful—and it may also decrease intracranial pressure.

However, intra-cranial pressure is relatively independent of gravity in this closed system. Similarly, in an open system, at the peak of Mont Blanc (15,771 feet or 4,807 meters), in the Alps, the atmospheric pressure is about half of what it is at sea level —yet a ball-point pen, if dropped, still falls to the ground at nearly the same speed—under the influence of gravity [2].

A group of Norwegian investigators [5] recently reported on a cohort of healthy volunteers in whom they studied sleep deprivation, a condition during which the top half of the brain has been sitting on the bottom half for too long—possibly resulting in excessive gravitational ischemia. They used novel brain MRI techniques to examine the white matter microstructure of subjects compared to a control group.

The Norwegian investigators found significant white matter changes during sleep deprivation compared to during a normal sleep/wake cycle—which they considered to represent changes in axonal diffusivity [2,5].

Autoregulation is a mechanism by which cerebral blood flow is maintained—primarily through regional vasoconstriction and vasodilation within the brain. It does not respond well to physical barriers such as intravascular clot or extravascular mass lesion. Gravity behaves as an extravascular mass lesion because it forces extravascular skull or brain tissue to push against the external walls of the blood vessels.

CONFLICT OF INTEREST

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

ACKNOWLEDGMENTS

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Gravity-induced ischemia in the brain and prone positioning for COVID-19 patients breathing spontaneously: still far from the truth!

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Dear Editor:

In an observational study of patients admitted to the intensive care unit (ICU) [1], we showed that early application of prone positioning can improve severe hypoxemia and respiratory failure in coronavirus disease 2019 (COVID-19) patients with spontaneous breathing. In that study [1], we included 21 patients who underwent prone positioning within 6 hours following ICU admission and 17 control patients, and we concluded that early prone positioning can significantly improve severe hypoxemia. This improvement was not, however, associated with a reduction in the mortality rate or in the use of invasive mechanical ventilation (P>0.05 for both). The results of our study are confirmed by recent larger, single- and multi-center studies and meta-analyses [2]. Moreover, to the best of our knowledge, no cases of ischemia in the brain and/or neurological complications related to prone positioning have been reported. Jaster and Ottaviani [3] suggested that the absence of improvement in the rate of mortality, or in the need for mechanical ventilation, can be fundamentally explained by "gravitational ischemia in the brain" resulting from the mass effect of one part of the brain upon another in the earth's gravitational field. These authors suggested that an upright head position (or at least partially upright) may be required to relieve gravitational ischemia in the brainstem autonomic nuclei, thereby explaining the absence of a reduction in mortality rate or in the requirement of invasive mechanical ventilation. According to this proposal, gravity behaves as an extravascular mass lesion because it forces extravascular skull or brain tissue to push against the external walls of the blood vessels, leading to brain ischemia. The authors suggest that intermittently elevating the patient’s head by 30° may be helpful, as it may decrease intracranial pressure, prevent neurological complications, and improve the outcomes of these patients. Although we agree with Jaster and Ottaviani’s [3] hypothesis that gravitational consequences in the brain may contribute to delirium in the ICU in patients requiring sedation and invasive mechanical ventilation, we think that, for several reasons, this hypothesis cannot be applied in non-intubated patients with acute respiratory distress syndrome (ARDS) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

First, unlike severe patients requiring sedation and mechanical ventilation, the position of patients with spontaneous breathing is usually changed from supine to prone frequently (every 2 to 4 hours), as described in most published studies [1,2], and according to Jaster and Ottaviani [3], doing so can prevent brain ischemia because it is reversible in its early stages.
Moreover, as suggested by Jaster and Ottaviani [3], an upright head position (or at least partially upright), is usually used for all these patients. In fact, this position improves oxygenation in ARDS patients and was proposed as an alternative to the prone position [2].

Second, the application of the prone position leads to an increase in lung recruitability and alveolar recruitment, which causes ventilation-perfusion enhancement. As a consequence, early application of the prone position can improve severe hypoxemia and respiratory failure in COVID-19 patients with spontaneous breathing [1,2]. This improves brain oxygenation and can prevent brain ischemia. A prospectively designed, multicenter, international, randomized, open-label meta-trial with a large sample size (1,121 patients) [2] established that awake prone positioning application leads to a significant reduction in the incidence of treatment failure within 28 days of enrollment in patients with respiratory failure due to COVID-19. In this study, a longer mean daily duration of awake prone positioning (> 8 hours/day) was associated with treatment success at day 28 (prevention of intubation or death). For patients with acute respiratory distress requiring invasive mechanical ventilation with a partial pressure of oxygen in arterial blood/fractional percentage of inspired oxygen (PaO₂/FIO₂ ratio < 150 mm Hg, it was established that the application of prone positioning was associated with a significant reduction of mortality [4]. According to formal guidelines [4], prone positioning is recommended for at least 16 consecutive hours in ARDS patients with a PaO₂/FIO₂ ratio < 150 mm Hg to reduce mortality (grade 1+).

Third, it has been well established that the prone position improves heart function [5]. The application of the prone position leads to an increase in the cardiac preload and decreases the right ventricular afterload in patients with ARDS [5]. This results in an increase in cardiac output in patients with pre-load reserve, leading to positive macrocirculatory effects with enhanced organ blood flow (in particular to the brain) and oxygen delivery to the body. All these phenomena can prevent brain ischemia.

**Figure 1.** Impact of the prone position on brain perfusion and oxygenation. RV: right ventricular; V/Q: ventilation-perfusion.
Finally, it has been well established that severe hypoxia leads to endothelial dysfunction and thrombosis formation. The major improvement of hypoxemia following application of the prone position can prevent this dysfunction and, as a consequence, thrombosis formation and brain ischemia.

In conclusion, as summarized in Figure 1, the early application of prone positioning can improve severe hypoxemia and outcomes in COVID-19 patients with spontaneous breathing. By substantially improving hypoxemia and cardiac output, the prone position can prevent endothelial dysfunction and, as a consequence, thrombosis formation and brain ischemia.

CONFLICT OF INTEREST

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

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REFERENCES

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

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

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

5. Images in Critical Care
The images section must be of high scientific quality and value and provide didactic and self-explanatory lessons. Images must be unique and adhere to ethical standards with patient/relative approval when appropriate and ensure protection of patient identity and privacy.
The total text should not exceed 200 words. A maximum of five authors is permitted. Up to 5 references are allowed. No abstract is required.
The legend for the image should concisely present relevant clinical information, including a short description of the patient’s history, relevant physical and laboratory findings, clinical course, response to treatment (if any), and condition at last follow-up. All labeled structures in the image should be described and explained in the legend.
6. Other Publication Types
Other publication types such as guidelines, brief reports, and history articles may be accepted. The recommended format can be discussed with the Editorial Board.

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PEER REVIEW AND PUBLICATION PROCESS

1. Screening after Submission
1) Screening process will conducted after submission. If the manuscript does not fit the aims and scope of the Journal or does not adhere to the Instructions to authors, it may be returned to the author immediately after receipt and without a review.
2) Before reviewing, all submitted manuscripts are inspected by Similarity Check powered by iThenticate (https://www.crossref.org/services/similarity-check/), a plagiarism-screening tool. If a too high a degree of similarity score is found, the Editorial Board will do a more profound content screening.
3) The criterion for similarity rate for further screening is usually 15%; however, the excess amount of similarity in specific sentences may be also checked in every manuscript. The settings for Similarity Check screening are as follows:
   It excludes quotes, bibliography, small matches of 6 words, small sources of 1%, and the Methods section.

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1) Submitted manuscripts will be reviewed by 2 or more experts in the corresponding field. The Editorial Board may request authors to revise the manuscripts according to the reviewer’s opinion. After revising the manuscript, the author should upload the revised files with a reply to each item of the reviewer’s opinion. The revised part should be marked as red font with underline.
2) The author’s revisions should be completed within 30 days after the request. If it is not received by the due date, the Editorial Board will not consider it for publication again.
3) The manuscript review process can be finished the second review. If further revision is requested, the Editorial Board may consider it.
4) The Editorial Board may request authors to correct English to reach a certain standard and authors should accept the request.
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6. Clinical Data Sharing Policy
Check List for Authors

A. Confirmation by authors

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<tr>
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<th>Check points</th>
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<td>Originality</td>
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<td>Research ethics</td>
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<td>English proofreading</td>
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</table>

B. Structure of article

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</tr>
</thead>
<tbody>
<tr>
<td>Sequence</td>
<td>☐ Title page, abstract and keywords, main text, conflict of interest, (acknowledgments), references, table, table legends, figure legends</td>
</tr>
<tr>
<td>Title page</td>
<td>☐ Title: The title should be concise and precise. The first letters of nouns, adjectives, verbs, and adverbs in titles should be capitalized. The title should use generic drug names, not brand names.</td>
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**Original Article**

☐ Manuscripts include an Abstract, Key Words, Introduction, Materials and Methods, Results, Discussion, Conflict of Interest, (Acknowledgments), References, Table(s), and Figure(s) in the order listed.

**Letters to the Editor**

☐ Letters to the Editor should include brief constructive comments that concern a published article; a short, free-standing opinion; or a short, interesting case.
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<td><strong>Letters to the Editor</strong></td>
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<td><strong>Images in Critical Care</strong></td>
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<td>☐ All tables and figures are provided in English, and all abbreviations are explained.</td>
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<tr>
<td><strong>Original Article</strong></td>
<td>☐ The text is organized into Introduction, Materials and Methods, Results, Discussion, (Acknowledgments), References.</td>
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<td>☐ The Materials and Methods section provides information on permission obtained from my affiliation and from patients for a human trial or animal testing.</td>
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<td>☐ The Discussion section is not a summary of results, but describes new and important findings without any duplicate contents.</td>
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<td><strong>Images in Critical Care</strong></td>
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<td>☐ The titles of tables start with “Table 1.” Footnotes should be provided consecutively in order of the information, statistics, and abbreviations.</td>
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<tr>
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<td>☐ In microscopic pictures, staining methods and magnification ratio should be indicated.</td>
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<td>☐ Copyright transfer form has been signed by all authors.</td>
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