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1. Xue J, et al. Received from the American College of Cardiology Foundation on behalf of the American Heart Association. Circulation. 2023;148(2):136-146. doi:10.1161/CIRCULATIONAHA.123.066550

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

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Impact of institutional case volume on intensive care unit mortality

Christine Kang, Ho Geol Ryu

Department of Anesthesiology and Pain Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea

The primary aim of this review is to explore current knowledge on the relationship between institutional intensive care unit (ICU) patient volume and patient outcomes. Studies indicate that a higher institutional ICU patient volume is positively correlated with patient survival. Although the exact mechanism underlying this association remains unclear, several studies have proposed that the cumulative experience of physicians and selective referral between institutions may play a role. The overall ICU mortality rate in Korea is relatively high compared to other developed countries. A distinctive aspect of critical care in Korea is the existence of significant disparities in the quality of care and services provided across regions and hospitals. Addressing these disparities and optimizing the management of critically ill patients necessitates thoroughly trained intensivists who are well-versed in the latest clinical practice guidelines. A fully functioning unit with adequate patient throughput is also essential for maintaining consistent and reliable quality of patient care. However, the positive impact of ICU volume on mortality outcomes is also linked to complex organizational factors, such as multidisciplinary rounds, nurse staffing and education, the presence of a clinical pharmacist, care protocols for weaning and sedation, and a culture of teamwork and communication. Despite some inconsistencies in the association between ICU patient volume and patient outcomes, which are thought to arise from differences in healthcare systems, ICU case volume significantly affects patient outcomes and should be taken into account when formulating related healthcare policies.

Key Words: institutional case volume; mortality; patient outcome

INTRODUCTION

According to the 2021 National Health Insurance Service data, Korea has 9,174 beds in 863 intensive care units (ICUs), excluding neonatal ICUs. Approximately half of these ICU beds are located in and around the capital, Seoul. The latest report on the Improvement Study on Assessment of the Appropriateness of Intensive Care Units, commissioned by the Health Insurance Review and Assessment Service (HIRA), revealed significant disparities in the quality of care and services provided depending on the region and hospital. Several hospitals reported substandard clinical outcomes, such as ICU mortality, when compared to other hospitals in Korea and international standards [1]. In 2020, HIRA reported an overall ICU mortality rate...
of 14.2% in Korea [2], which was higher than the 9% rate in Canada [3] and the 11.3% rate in the US [4].

Numerous factors are associated with ICU mortality, such as age, sex, comorbidities, the utilization of mechanical ventilation, renal replacement therapy (RRT), and vasopressors. From a healthcare system perspective, ICU case volume plays a crucial role in patient outcomes, in conjunction with admission route, the degree of critical care nursing, and a multidisciplinary ICU team. Critically ill patients require specialized and intensive treatment/management, which is provided by professionals with expertise in various relevant fields. Common diagnoses in the ICU, such as sepsis, acute respiratory distress syndrome, and circulatory shock, often demand continuous patient monitoring, mechanical ventilation, continuous RRT, and even extracorporeal membrane oxygenation, sometimes all simultaneously. To optimize the management of critically ill patients, intensivists should be well-trained and familiar with the most recent clinical practice guidelines. In order to maintain a consistent and reliable quality of patient care, an efficiently functioning unit with adequate patient throughput is ideal, which can be assessed as case volume. Numerous studies have examined the impact of hospital case volume for various procedures and settings, including high-risk surgical procedures [5], emergent procedures [6], solid organ transplantation [7,8], and trauma [9]. These studies have consistently reported improved patient outcomes with higher institutional case volumes. The precise mechanism underlying this association remains unclear, but it is thought to result from the cumulative experience of providers and selective referral to institutions with better outcomes. Although the reasons behind the association between ICU patient volume and mortality are not fully understood, the majority of studies have reported a positive correlation between institutional ICU patient volume and patient survival.

METHODS

A PubMed search was conducted using the terms "intensive care," "critical care," "case volume," "outcome," and "mortality" to identify relevant papers on this topic until February 13, 2023. Additionally, the reference lists of review papers and published systematic reviews were examined to ensure that no pertinent articles were missed during the electronic search.

KEY MESSAGES

- Higher intensive care unit case volume is associated with improved patient mortality.
- Healthcare system policies should take into account the impact of case volume on the outcomes of critically ill patients.

THE IMPACT OF INSTITUTIONAL CASE VOLUME ON VARIOUS CRITICALLY ILL PATIENT POPULATIONS

Tables 1-3 summarized studies that evaluated the impact of ICU case volume on patient outcome in general critically ill patients (Table 1) [10-13], sepsis and septic shock patients (Table 2) [14-19], and mechanically ventilated patients (Table 3) [20-26].

Critically Ill Patients in General

A prospective study published in 2004 analyzed 12,615 patients across 89 European ICUs over a four-month period to determine whether a correlation existed between ICU case volume and mortality. The results revealed an inverse relationship between ICU volume and in-hospital mortality (odds ratio [OR], 0.97; 95% confidence interval [CI], 0.95–0.99; P<0.0005), although the clinical relevance was small. A sub-analysis of patients with a Simplified Acute Physiology Score (SAPS) II higher than 32 demonstrated a stronger association between ICU case volume and in-hospital mortality (OR, 0.83; 95% CI, 0.78–0.89; P<0.0001). The study’s most important finding was that in-hospital mortality was notably higher in ICUs with an average occupancy rate exceeding 80% than in those with occupancy rates below 80% (OR, 1.32; 95% CI, 1.13–1.55; P<0.0004) [10]. The authors concluded that a high volume of high-risk patients might be a prerequisite for higher-quality care, provided that the occupancy rate remains reasonable.

A study of 83,259 ICU patients in 40 ICUs in Austria between 1988 and 2005 revealed that a higher patient turnover was associated with a reduced risk of in-hospital mortality (OR, 0.960; 95% CI, 0.946–0.974; P-value, not provided). Additionally, an increased patient-to-nurse ratio (more assigned patients per nurse) was also associated with an increased risk of in-hospital mortality (OR, 1.30; 95% CI, 1.21–1.39; P-value, not provided) [11]. The authors proposed a non-linear relationship between ICU volume and mortality improvement; specifically, they...
Table 1. The impact of ICU volume on critically ill patients in general

<table>
<thead>
<tr>
<th>Study</th>
<th>Published year</th>
<th>No. of patients</th>
<th>No. of centers and ICUs</th>
<th>Outcome</th>
<th>Volume category (case/year)</th>
<th>Suggested cut-off threshold</th>
<th>Impact of case volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lapichino et al.</td>
<td>2004</td>
<td>12,615</td>
<td>Not reported, 89 ICUs</td>
<td>In-hospital mortality</td>
<td>Not reported</td>
<td>None</td>
<td>Significant</td>
</tr>
<tr>
<td>Metnitz et al.</td>
<td>2009</td>
<td>83,259</td>
<td>Not reported, 40 ICUs</td>
<td>In-hospital mortality</td>
<td>Not categorized</td>
<td>420 Patients per year</td>
<td>Significant</td>
</tr>
<tr>
<td>Glance et al.</td>
<td>2006</td>
<td>70,757</td>
<td>76 Centers, 92 ICUs</td>
<td>In-hospital mortality</td>
<td>Low, &lt;134 Medium, 134–216 High, 217–295 Very high, &gt;295</td>
<td>None</td>
<td>Significant (for high risk patients)</td>
</tr>
<tr>
<td>Sasabuchi et al.</td>
<td>2015</td>
<td>&gt;1,000 Centers, not reported</td>
<td></td>
<td>In-hospital mortality</td>
<td>Low, &lt; 497 Intermediate, 497–748 High, &gt;747</td>
<td>None</td>
<td>Significant (12.3% vs. 7.5%)</td>
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ICU: intensive care unit.

Table 2. Impact of ICU volume on patients with sepsis and septic shock

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<tr>
<th>Study</th>
<th>Published year</th>
<th>No. of patients</th>
<th>No. of centers and ICUs</th>
<th>Outcome</th>
<th>Volume category (case/year)</th>
<th>Suggested cut-off threshold</th>
<th>Impact of case volume</th>
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<td>Peelen et al.</td>
<td>2007</td>
<td>4,605</td>
<td>Not reported, 28 ICUs</td>
<td>In-hospital mortality</td>
<td>Not specified</td>
<td>None</td>
<td>Significant</td>
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<tr>
<td>Zuber et al.</td>
<td>2012</td>
<td>3,437</td>
<td>Not reported, 41 ICUs</td>
<td>ICU and hospital mortality</td>
<td>Low, &lt;5 Medium, 5–12 High, &gt;12</td>
<td>None</td>
<td>Significant (ICU mortality, 64.9% vs. 57.6%)</td>
</tr>
<tr>
<td>Shahin et al.</td>
<td>2012</td>
<td>30,727</td>
<td>170 Centers, 170 ICUs</td>
<td>In-hospital mortality</td>
<td>Q1, 59–75 Q2, 95–103 Q3, 121–138 Q4, 168–206</td>
<td>None</td>
<td>Insignificant (42.7% in Q1 vs. 39.0% in Q4)</td>
</tr>
<tr>
<td>Maharaj et al.</td>
<td>2021</td>
<td>273,001</td>
<td>Not reported, 231 ICUs</td>
<td>ICU and hospital mortality</td>
<td>Q1, 12–177 Q2, 178–242 Q3, 243–334 Q4, 335–744</td>
<td>215 Patients per year</td>
<td>Significant (ICU mortality, 23.4% in Q1 vs. 21.5% in Q4)</td>
</tr>
<tr>
<td>Chen et al.</td>
<td>2022</td>
<td>134,046</td>
<td>1,902 Centers, not reported</td>
<td>In-hospital mortality</td>
<td>Q1, 1–13 Q2, 14–32 Q3, 33–75 Q4, &gt;75</td>
<td>40 patients per year</td>
<td>Significant (24% in Q1 vs. 18% in Q4)</td>
</tr>
<tr>
<td>Naar et al.</td>
<td>2022</td>
<td>10,716</td>
<td>Not reported</td>
<td>ICU mortality</td>
<td>(Total volume) High, 6,758 Medium high, 2,608 Medium low, 1,078 Low, 272</td>
<td>None</td>
<td>Insignificant</td>
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ICU: intensive care unit; Q: quartile.

suggested a U-shaped relationship, where mortality rates initially decrease as patient volume increases, but beyond a certain point (n=450), mortality rates begin to increase again. This implies that an excessive number of patients cared for, even in highly experienced institutions, may result in worse outcomes, offsetting the positive impact of higher case volume.

A retrospective cohort study of 70,757 patients admitted to ICUs in the US from 2001 to 2003 reported an overall mortality rate of 14.6%. While the impact of institutional case volume could not be determined, institutions that managed a higher number of severely critically ill patients (>295 patients per year with SAPS II scores above 30) demonstrated better outcomes than centers with a lower volume of high-risk patients (OR, 0.77; P=0.047) [12].
A similar study involving 596,143 ICU patients from 2007 to 2012 reported overall ICU and hospital mortality rates of 4.8% and 9.9%, respectively. The ICU volume was categorized into high (≥748 patients per year), intermediate (497–747 patients per year), and low (≤496 patients per year) volume groups. Both a higher ICU volume (OR, 0.77; 95% CI, 0.66–0.89; P=0.001) and a higher ICU-to-hospital bed ratio (OR, 0.82; 95% CI, 0.71–0.94; P=0.005) were significant factors in reducing hospital mortality. When the subgroup analysis was stratified by the ICU-to-hospital bed ratio, the volume-mortality relationship was significant only in the high ICU-to-hospital bed ratio group (high, ≥2.96% vs. low, ≤1.74%; OR, 0.74; 95% CI, 0.58–0.93; P=0.009) [13]. In this study, the group with the lowest ICU-to-hospital bed ratio exhibited the highest illness severity (patients requiring mechanical ventilation, RRT, or vasopressor use) compared to the high ratio group. Due to a shortage of ICU beds, only severely ill patients could be admitted to the ICU, which may have led to worse outcomes and minimized the overall effect of ICU volume.

### Sepsis and Septic Shock Patients

Patients requiring intensive care for sepsis and septic shock also exhibit a similar inverse relationship between institutional ICU case volume and mortality. In 2021, a cohort study involving 273,001 sepsis patients from 231 ICUs in the UK demonstrated that ICUs with higher annual sepsis case volumes had significantly lower hospital mortality rates compared to centers with lower case volumes (OR, 0.89; 95% CI, 0.82–0.96; P=0.002) [17]. The study suggested an annual sepsis ICU patient case volume threshold of 215 patients per ICU per year for favorable outcomes, without specifying an upper threshold value [17]. A similar relationship between ICU volume and mortality benefits has been observed in cancer patients suffering from septic shock. A 12-year (1997–2008) retrospective cohort study, which included 3,437 septic shock patients with malignancies across 41 ICUs, revealed that high-volume units (>12 patients per year, median of 614 total ICU patients per year) had a significantly lower ICU mortality rate than low-volume units (<5 patients per year, median of 614 total ICU patients per year) (OR, 0.63; 95% CI, 0.46–0.87; P=0.002) [15].

An analysis of 134,046 septic shock patients from 1,902 hospitals in China during a 1-year study in 2020 revealed that, although there was no significant difference in overall ICU mortality between septic shock volume quartiles, hospital
mortality for septic shock cases was significantly reduced in the highest quartile of septic shock case volume ($\beta=-0.86$; 95% CI, -0.98 to -0.74; $P<0.001$) [18]. Study participants were divided into quartiles based on their annual septic shock case volume in the ICU. The fourth quartile group had a mean ICU case volume of 1,463 ± 2,119 per year and a septic shock volume of >75 cases per year, while the first quartile group had a mean ICU volume of 414±1,509 per year and a septic shock volume of 1–13 cases per year. The suggested volume threshold associated with a favorable hospital mortality rate was 40 septic shock cases per year, which differs from the previously mentioned UK results, which had a volume threshold of 215 cases per year.

In line with previous studies, an evaluation of 4,065 severe sepsis patients across 28 ICUs in the Netherlands demonstrated a significant association between the annual number of severe sepsis patients and risk-adjusted in-hospital mortality (OR, 0.97; 95% CI, 0.94–0.99; $P=0.029$) [14]. Although there was a positive relationship between volume and outcome, the authors argued that due to the weak correlation compared to elective surgical procedures, it may not be feasible or beneficial to plan admissions for severe sepsis or transfer patients to higher volume centers [14]. A meta-analysis of 11 studies involving septic ICU patients found a significant association between a higher annual case volume and lower mortality (OR, 0.76; 95% CI, 0.65–0.89; $P=0.001$) [27]. A subsequent dose-response analysis suggested that the mortality benefit plateaus at an annual case volume of 400 cases [27].

The reported ICU and hospital mortality rates for patients with sepsis are 25.8% and 35.3%, respectively, with relevant independent risk factors for in-hospital mortality including the use of mechanical ventilation and RRT [15,28]. A study of ICUs in Finland found a similar association among 1,558 patients who underwent RRT in 23 ICUs. Patients were classified into tertiles based on the annual case volume of RRT: low (18 [16–22]), medium (28 [25–30]), and high (54 [56–77]) volume. In-hospital mortality was significantly higher in low-volume ICUs than in high-volume ICUs (OR, 2.06; 95% CI, 1.49–2.84; $P=0.001$) [29].

In the UK, a study of 33,538 adult severe sepsis patients from 2008 to 2009 was conducted, involving 170 ICUs in 170 centers. These patients were categorized into quartiles and evaluated for differences in mortality [16]. The annual median volume of severe sepsis patients was 70 (59–75) in quartile 1, 98 (95–103) in quartile 2, 130 (121–138) in quartile 3, and 190 (168–206) in quartile 4. No relationship was found between the annual se-

vere sepsis patient volume and in-hospital mortality ($P=0.65$). A more recent study in the US reported conflicting results. An analysis of 10,716 sepsis patients showed that ICU and hospital mortality was similar between centers with lower volume (136 cases of sepsis per year) and centers with high volume (3,379 cases of sepsis per year) (OR, 0.98; 95% CI, 0.46–2.08; $P=0.962$). Centers with lower volume ICUs were less likely to utilize RRT (OR, 0.57; 95% CI, 0.44–0.73; $P=0.001$) [19]. It can be speculated that high-volume centers are more likely to care for critically ill patients with greater disease severity.

**Patients Requiring Mechanical Ventilation**

During the 10 years between 2007 and 2016, 158,712 adult ICU patients who required mechanical ventilation for at least 48 hours were treated in 55 centers across Korea. These patients were divided into three groups based on the annual number of patients at each center: low volume (<300), medium volume (300–500), and high volume (>500). The in-hospital mortality rates for the low-, medium-, and high-volume groups were 39.2%, 35.8%, and 32.6%, respectively ($P<0.01$). After adjusting for covariates, the low-volume centers exhibited a significantly higher mortality rate than the high-volume centers (OR, 1.33; 95% CI, 1.30–1.37; $P<0.001$) [26]. A similar inverse relationship between case volume and long-term mortality was observed when comparing 5-year mortality rates between low- and high-volume centers (OR, 1.26; 95% CI, 1.20–1.31; $P<0.001$).

A study analyzing 20,214 patients in medical ICUs who received mechanical ventilation between 1988 and 2010 was conducted. After adjusting for relevant risk factors, it was found that higher hospital volume (>400 patients per year) was significantly associated with lower ICU and hospital mortality (OR, 0.63; 95% CI, 0.50–0.79; $P<0.001$ and OR, 0.66; 95% CI, 0.52–0.83; $P<0.001$) compared to lower hospital volume (<150 patients per year). The risk-adjusted, predicted ICU and hospital mortality rates were 14.5% and 25.5%, respectively, in higher volume centers, and 21.2% and 34.2%, respectively, in lower volume centers [20]. The impact of case volume on 14,440 acute exacerbation of chronic obstructive pulmonary disease (AECOPD) patients in 31 medical ICUs was assessed. ICU and hospital mortality rates were lower in higher-volume units (16.0% and 21.2%, respectively, in units with more than 47 admissions per year) compared to lower-volume units (18.3% and 22.7%, respectively, in units with fewer than 25 admissions per year), with an OR of 0.90 (95% CI, 0.75–1.09; P-value, not provided) [22]. The use of non-invasive ventilation (NIV) in AECOPD patients also varied according to case volume. Ad-
mission to higher volume units was associated with a greater likelihood of using NIV (OR, 1.17; 95% CI, 1.07–1.28; P-value, not provided) [22]. The authors suggested that the mortality benefit in higher volume units could be attributed to the increased use of NIV in these units and possibly differences in the nurse-to-bed ratio, despite the lack of data on this aspect in the study.

Several studies from countries with different healthcare systems have reported conflicting results. A retrospective cohort study of 208,810 mechanically ventilated patients from 136 ICUs in Australia and New Zealand demonstrated that the risk of in-hospital mortality was higher in centers with the highest volume (801–932 patients per year) compared to centers with the lowest volume (12–101 patients per year) (OR, 1.16; 95% CI, 1.06–1.28; P=0.009) [23]. In contrast, a Canadian study that included both medical and surgical patients requiring mechanical ventilation did not show a significant volume-mortality association. Instead, it found a less significant increase in mortality in the lowest-volume centers (<100 cases per year) compared to the highest-volume centers (>700 cases per year) (OR, 1.13; 95% CI, 0.87–1.47; P-value, not provided) [24].

**DISCUSSION**

Most studies on ICU patients have suggested that an increase in case volume positively impacts mortality outcomes for patients who are generally ill in the ICU, including those with sepsis, septic shock, and those requiring mechanical ventilation. Several studies have proposed a threshold volume at which the lowest mortality is achieved; however, both below and above this threshold, mortality begins to increase, demonstrating a U-shaped relationship between case volume and mortality. Interestingly, a few countries with different healthcare systems, such as the UK, Australia, and Canada, have not shown similar impacts of volume on mortality improvement.

Traditionally, the volume-mortality effect has been attributed to the accumulation of clinical experience and selective referral. High-volume institutions are more likely to employ experienced personnel who can readily detect patient deterioration and have access to the various resources needed to manage critically ill patients. The presence of trained intensivists and high-intensity ICU staffing has already been associated with improved mortality rates and reduced ICU and hospital lengths of stay [30]. In 2015, Korea implemented a mandate requiring doctor presence and reimbursement incentives for intensivist presence in ICUs at tertiary centers. Prior to this implementation, fewer than one-third of ICUs had intensive care specialists working a 5-day week [31]. However, by 2020, this number increased to 46.7% [2]. A study examining the implementation of intensivists in 441 Korean ICUs found significant decreases in both ICU and 90-day mortality rates (11.7% to 6.3%, respectively, P=0.047; 18.6% to 10.3%, respectively, P=0.012) and a hazard ratio for 90-day mortality of 0.39 (95% CI, 0.23–0.67; P=0.001) [32]. Despite the improved mortality rates following the implementation of intensivist-led teams, the proportion of ICUs with full-time intensivists remains significantly lower than international standards. A 2011 study of ICUs in Asia found that 66% of the 150 ICUs surveyed had 24-hour intensivist coverage [33], while only 26.9% of Korean ICUs in 2020 were fully staffed by intensivists [2]. As a result, discrepancies in clinical outcomes by region and hospital persist in Korea. Depending on hospital volume, tertiary, general, and primary hospitals in Korea have demonstrated 5-year mortality rates for mechanically ventilated patients of 37%, 55%, and 82%, respectively. Hospitals with the presence of intensivists or those located in the capital tend to exhibit lower mortality rates [2].

Selective referral is a phenomenon where patients are more likely to be referred to high-volume centers, particularly for complex surgical procedures, pediatric surgery, and trauma. However, it has been suggested that more complex organizational factors may be associated with improved outcomes in critically ill patients. Factors such as multidisciplinary rounds, ICU nurse staffing and education, the presence of a clinical pharmacist, protocols for weaning and sedation, and a culture of teamwork and communication may all contribute to enhancing ICU patient outcomes [34,35]. Clinical pharmacists can offer valuable consultation in developing plans for drug dosing and monitoring, as well as assisting in medication reconciliation upon patient discharge [36-38]. In a database review of 199,082 Medicare patients treated in 961 hospitals with vancomycin and aminoglycosides, hospitals where pharmacists monitored the use of these drugs demonstrated lower mortality rates, shorter lengths of stay, and fewer adverse events [39].

The design of Korea’s healthcare system does not provide adequate reimbursements for managing critically ill patients. When comparing results from different healthcare systems, caution should be exercised, as the impact of relevant factors may be biased or obscured. One prime example is ICU case volume, as the suggested cut-off may differ between densely
populated regions or countries (such as Korea) and sparsely populated countries (such as Australia). Measures proven to improve patient outcomes, such as dedicated intensivists, higher nurse-to-patient ratios, and multidisciplinary care teams that include nutritionists, pharmacists, and physical therapists, are often overlooked. The discrepancy in the results of the Australian/New Zealand data [21] from previous studies of volume-mortality association may stem from differences in health system jurisdictions, which was also identified in results from countries in similar situations, such as Canada [24] and the UK [25]. The authors of the 2021 UK study suggest that the unique nature of the US healthcare system, which has complex funding sources compared to the publicly funded healthcare systems of Canada, Finland, or the UK, may contribute to disparities in access to care and thereby lead to weak or nonexistent associations between sepsis patient volume and clinical outcomes [17]. Private-sector US hospitals are primarily funded through fee-for-service and prospective payment charges, which are reimbursed by private insurance companies, Medicare, state Medicaid programs, and other government funds. This contrasts with Canada and other countries that have publicly funded single-payer healthcare insurance. After adjusting for clustering and the procedure or condition studied, the relative odds of Canada showing a significant volume-outcome association compared to the US were substantially low (OR, 0.23; 95% CI, 0.07–0.76; P=0.01) [40].

The observed center volume effect on specific types of surgeries and patient populations, which demonstrates improved patient mortality, has prompted discussions about whether these procedures should be limited to high-volume centers with favorable outcomes [41,42]. The significant volume effect on mortality in solid organ transplantation and trauma centers has led to policy changes requiring minimum case volumes for center accreditation. In some countries, an enhanced patient referral system that clusters low- and high-volume centers in close proximity is already being implemented [16]. However, it remains debatable whether a similar volume effect exists in critically ill patients, as volume effects have shown inconsistent results. A possible explanation for this inconsistency may be that institutions with higher patient volumes are more likely to adopt newly accredited best practices. For example, the previously mentioned study regarding ICU-admitted AECOPD patients [22] showed that units with higher volumes were more likely to implement NIV, which was associated with improved survival rates. When institutions with higher volumes demonstrate better outcomes by implementing new evidence-based practices, it becomes more likely that these practices will be adopted across all hospitals, leading to an attenuation of the volume and outcome association [20,43].

There is considerable diversity among patients admitted to the ICU. The current inconsistencies in the relationship between ICU case volume and outcomes necessitate a multi-layered study focusing on ICU patients with specific diagnoses. Another aspect that warrants a thorough analysis is the intensivist-to-patient ratio. A recent US study on intensivist-to-patient ratios examined the outcomes of 51,656 patients under the care of 246 intensivists. The average caseload was 11.8 patients per day, with no evident association between the intensivist-to-patient ratio and mortality (hazard ratio for each additional patient: 0.987; 95% CI, 0.97–1.01; P=0.2) [44]. In Korea, the average caseload per intensivist was 44.7 patients per day in 2014, which steadily decreased to 22.2 patients per day in 2021 [1]. Further prospective studies are needed to assess the impact of the intensivist-to-patient ratio.

In conclusion, despite a few inconsistencies, a higher ICU case volume has been demonstrated to positively impact mortality rates. Given the significant effect on patient outcomes, institutional ICU case volume should be taken into account when developing healthcare policies related to this area.

CONFLICT OF INTEREST

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

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ORCID

Christine Kang https://orcid.org/0000-0003-3974-9046
Ho Geol Ryu https://orcid.org/0000-0001-8952-6049
AUTHOR CONTRIBUTIONS

Conceptualization: HGR. Data curation: CK. Methodology: HGR. Validation: HGR. Investigation: CK. Writing–original draft: all authors. Writing–review & editing: all authors.

REFERENCES


Comparison of safety and efficacy between therapeutic or intermediate versus prophylactic anticoagulation for thrombosis in COVID-19 patients: a systematic review and meta-analysis

Hyeon-Jeong Lee1*, Hye Jin Jang2*, Won-II Choi2, Joonsung Joh3, Junghyun Kim3, Jungeun Park1, Miyoung Choi1

1Division of Healthcare Technology Assessment Research, National Evidence-based Healthcare Collaborating Agency, Seoul, Korea
2Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Myongji Hospital, Hanyang University, Korea
3Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, National Medical Center, Seoul, Korea

Background: Patients with coronavirus disease 2019 (COVID-19) infections often have macrovascular or microvascular thrombosis and inflammation, which are known to be associated with a poor prognosis. Heparin has been hypothesized that administration of heparin with treatment dose rather than prophylactic dose for prevention of deep vein thrombosis in COVID-19 patients.

Methods: Studies comparing therapeutic or intermediate anticoagulation with prophylactic anticoagulation in COVID-19 patients were eligible. Mortality, thromboembolic events, and bleeding were the primary outcomes. PubMed, Embase, the Cochrane Library, and KMbase were searched up to July 2021. A meta-analysis was performed using random-effect model. Subgroup analysis was conducted according to disease severity.

Results: Six randomized controlled trials (RCTs) with 4,678 patients and four cohort studies with 1,080 patients were included in this review. In the RCTs, the therapeutic or intermediate anticoagulation was associated with significant reductions in the occurrence of thromboembolic events (5 studies, n=4,664; relative risk [RR], 0.72; P=0.01), and a significant increase in bleeding events (5 studies, n=4,667; RR, 1.88; P=0.004). In the moderate patients, therapeutic or intermediate anticoagulation was more beneficial than prophylactic anticoagulation in terms of thromboembolic events, but showed significantly higher bleeding events. In the severe patients, the incidence of thromboembolic and bleeding events in the therapeutic or intermediate.

Conclusions: The study findings suggest that prophylactic anticoagulant treatment should be used in patients with moderate and severe COVID-19 infection groups. Further studies are needed to determine more individualized anticoagulation guidance for all COVID-19 patients.

Key Words: anticoagulants; COVID-19; thromboembolism; thrombosis

INTRODUCTION

Patients hospitalized for coronavirus disease 2019 (COVID-19) often have macrovascular and microvascular thrombosis and inflammation. In such cases, the prognosis is poor [1,2].
Several mechanisms have been identified for the increased thrombotic risk, and many patients hospitalized for COVID-19 further develop a cytokine storm, which leads to hyperinflammation, endothelial injury, platelet activation, and coagulopathy [3]. In addition, unlike most critically ill patients, venous thromboembolism often occurs in COVID-19 patients despite the use of thromboprophylaxis [4]. Thus, in severe cases of COVID-19 infection, systemic inflammation and coagulopathy occur with test findings similar to those of disseminated intravascular coagulation [5,6]. The anticoagulants used in most studies included unfractionated heparin, low-molecular-weight heparin, and direct oral anticoagulant. In this study, a therapeutic dose refers to a dose administered to patients with deep vein thrombosis (DVT), a prophylactic dose refers to a dose used as prophylactic therapy in patients without DVT, and an intermediate dose is between the amount of therapeutic and the prophylactic dose. Heparin has antithrombotic, anti-inflammatory, and antiviral properties [7-9]. Therefore, it has been hypothesized that administration of heparin with treatment dose would be more beneficial rather than prophylactic dose for DVT prevention in COVID-19 patients. This meta-analysis reviewed the anticoagulant effects and safety of heparin according to the doses given using current data on thrombotic risk, bleeding and mortality of COVID-19 patients admitted to general wards and intensive care units (ICUs).

MATERIALS AND METHODS

This systematic review and meta-analysis were performed according to the recommendations outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10] (Supplementary Table 1). This study was registered in the Prospective Register of Systematic Reviews (registration no. CRD42022347827).

Eligibility Criteria

The inclusion criteria were as follows: (1) studies targeting patients with confirmed COVID-19; (2) studies comparing therapeutic doses including intermediate doses of an anticoagulant to prophylactic anticoagulant administration; (3) studies reporting mortality, thromboembolic events, and bleeding, etc.; (4) studies published after 2020; (5) randomized controlled trials (RCTs) or observational studies with a comparison group; and (6) written in English or Korean languages. The exclusion criteria were as follows: (1) studies that did not target patients with confirmed COVID-19; (2) studies on animal models; and (3) duplicated studies.

Information Sources and Search Strategy

We developed search strategies with the help of a librarian and clinical experts and searched Ovid Medline, Ovid Embase, the Cochrane Central Register of Controlled Trials, and KMbase as a Korean domestic database in July 2021. Search terms related to COVID-19 were used, including “coronavirus,” “novel coronavirus,” “novel coronavirus 2019,” “2019 nCoV,” “COVID-19,” “Wuhan coronavirus,” “Wuhan pneumonia,” “SARS-CoV-2,” “thromboembolism,” “anticoagulation,” and “heparin.” The search strategy is presented in Supplementary Table 2.

Selection Process

Four authors (HJL, HJJ, JK, and JP) screened the retrieved citations by title and abstract in Covidence (https://www.covidence.org/) according to the inclusion/exclusion criteria. Full texts were assessed for final decisions regarding inclusion or exclusion. If an agreement was not reached between the authors, an agreement was reached through discussion with another author (MC).

Data Items and Extraction

The following data were extracted using a pre-defined data abstraction form: author, publication year, study design, study country, study setting, the severity of COVID-19, number in each arm, anticoagulation regimen, and outcomes of interest. Three authors (HJL, HJJ, and JP) performed data extraction and another two authors (WIC and JK) checked the data independently.

Study Outcomes

The primary outcomes were mortality, thromboembolic events, and adverse events such as bleeding. The secondary

KEY MESSAGES

- The mortality rate of patients with moderate coronavirus disease 2019 (COVID-19) receiving therapeutic and prophylactic anticoagulants was similar.
- Patients receiving therapeutic doses showed benefits in preventing thromboembolism but more occurrence of bleeding compared to the prophylactic group.
- In patients with severe COVID-19, there were no differences in mortality, thromboembolism, or bleeding between the therapeutic group and prophylactic group.
outcomes were the need for mechanical ventilation (MV), duration of MV, hospital discharge, and length of stay (LOS) in the hospital or ICU.

**Study Risk of Bias Assessment**
To evaluate the risk of bias in the eligible studies, Cochrane’s Risk of Bias (RoB) 1.0 [11] tool was used for RCTs, and the Risk of Bias Assessment tool for Non-randomized Studies (RoBANS) 2.0 [12], which is an update of RoBANS 1.0 [13], was used for non-randomized studies. Quality assessments of the studies were conducted by two independent authors (WIC and JJ) and disagreements were resolved by a third author (MC).

**Effect Measures and Synthesis Methods**
To evaluate outcomes, we used relative risks (RRs) with a 95% confidence intervals (CIs) for discrete variables and mean differences (MDs) with 95% CIs for continuous variables. Forest plots were used for the graphical display of pooled estimates with 95% CIs. To deal with heterogeneity across the included studies, random-effects models were used. We considered I² statistics above 75% to indicate significant heterogeneity. We performed subgroup analysis based on patient severity and therapeutic or intermediate anticoagulation. To synthesize the data, we used RevMan Manager 5.4 4 (RevMan, The Cochrane Collaboration) as a meta-analysis statistical program.

**Certainty Assessment**
We evaluated the level of evidence of the primary outcomes using the Grading of Recommendations Assessment Development and Evaluation (GRADE) methodology [14]. Two authors (WIC and JJ) assessed the certainty of evidence as high, moderate, low, or very low, and discrepancies were resolved through discussions with a third author (MC).

**RESULTS**

**Study Selection**
A total of 11,079 records were identified using the literature search strategy. After excluding duplicates, the titles and abstracts of 9,659 records were screened. Of the 9,659 records, 292 reports were retrieved. After examining the full texts, we included six RCTs and four cohort studies in our review (Figure 1). The list of excluded studies and reasons for exclusion are presented in Supplementary Table 3.

**Study Characteristics**

**Mortality**
Six RCT studies reported mortality. The 28-day, 30-day, and in-hospital mortality (5 studies, n=4,673, RR=1.03; 95% CI, 0.91–1.16; I²=11%, P=0.63) [15,17-20] and 90-day mortality (1 study, n=562, RR=1.07; 95% CI, 0.89 –1.29) [16] were similar between the therapeutic or intermediate group and prophylactic group (Figure 2). Consistent results were obtained for subgroup analysis by severity (patients with moderate and severe COVID-19 infections) and subgroup analysis in the severe COVID-19 patient group comparing intermediate to prophylactic anticoagulation (Supplementary Figures 2 and 3). Three cohort studies reported mortality. Two synthesized studies [21,22] showed benefits in mortality in the therapeutic or intermediate group compared to prophylactic group (n=331, RR=0.63; 95% CI, 0.39 –1.00; I²=20%, P=0.05) (Figure 3) and one study [23] reported that therapeutic anticoagulation were associated with significant reductions in ICU mortality compared to prophylactic anticoagulation (log odds=−0.64; 95% CI,
Identification of studies via databases

11,079 Records identified from databases
2,441 PubMed
8,331 Ovid Embase
186 CENTRAL
121 KMbase

Records removed before screening: 1,420 Duplicate records removed

9,659 Records screened
9,367 Records excluded

292 Reports sought for retrieval
0 Reports not retrieved

292 Reports assessed for eligibility

282 Reports excluded
5 No population
22 No intervention
11 No comparator
8 No outcome
10 No study design: studies other than randomized controlled trials or observational studies with a comparator group
124 Other languages
99 Ongoing study
3 Duplicates

10 Studies included in review
10 Reports of included studies

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart.

Thromboembolic events
Five RCTs [15-19] reported the occurrence of thromboembolic events. Therapeutic or intermediate anticoagulation compared to prophylactic anticoagulation reduced the occurrence of thromboembolic events (n=4,664, RR=0.72; 95% CI, 0.56–0.93; I²=0%, P=0.01). Subgroup analysis showed that the therapeutic anticoagulation did not reduce thromboembolic events in the severe COVID-19 patient group, but did reduce thromboembolic events in the moderate COVID-19 patient group (Figure 4). In four cohort studies [21-24], the preventive effects on thromboembolic events were similar between the therapeutic or intermediate group and prophylactic groups (n=1,043, RR=0.67; 95% CI, 0.34–1.32; I²=78%, P=0.25) (Figure 5).

Bleeding
Five RCTs [15-19] reported major bleeding. The risk of major bleeding was significantly higher in the therapeutic or intermediate group compared to the prophylactic group (n=4,667, RR=1.88; 95% CI, 1.23–2.87; I²=0%, P=0.004). The risk of bleeding in the therapeutic group was higher in the subgroup of patients with moderate COVID-19 (n=2,841, RR=2.25; 95% CI, 1.19–4.27; I²=0%, P=0.01), but was similar in patients with severe COVID-19 (Figure 6). Three cohort studies [21-23] reported the risk of bleeding, which was similar between the therapeutic or intermediate group and prophylactic group (n=1,040, RR=0.69; 95% CI, 0.38–1.25; I²=0%, P=0.22) (Figure 7).

Secondary Outcomes
In the RCTs, the MV rate [17], MV duration [17], hospital discharge [15,17,19], and hospital LOS [17] were similar between the therapeutic group and prophylactic group. However, ICU LOS [20] was significantly shorter in the intermediate group compared to the prophylactic group (1 study, n=562; MD, −1 day; 95% CI, −1.98 to −0.02 day; P=0.05). In one cohort study [21], ICU LOS was similar between the therapeutic group and...
<table>
<thead>
<tr>
<th>First author (study)</th>
<th>Year</th>
<th>Study design</th>
<th>Country</th>
<th>Setting</th>
<th>Severity</th>
<th>Sample size (intervention/control)</th>
<th>Anticoagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATTACC investigators [15]</td>
<td>2021</td>
<td>RCT (REMAP-CAP, ACTIV-4a, ATTACC)</td>
<td>US, Canada, UK, Brazil, Mexico, Nepal, Australia, Netherlands, Spain</td>
<td>Multicenter</td>
<td>Moderate</td>
<td>1,181/1,050</td>
<td>Therapeutic dose - LMWH, according to patient weight</td>
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<td>REMAP-CAP investigators [19]</td>
<td>2021</td>
<td>-</td>
<td>-</td>
<td>Severe</td>
<td>534/564</td>
<td>- Alternative UFH, target for aPTT 1.5–2.5 times the upper limit of normal or anti-Xa levels (0.3–0.7 IU/ml)</td>
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<td>Bikdeli [16], Sadeghipour [20]</td>
<td>2021</td>
<td>RCT (INSPIRATION)</td>
<td>Iran</td>
<td>Multicenter</td>
<td>Severe</td>
<td>276/286</td>
<td>Intermediate dose - Enoxaparin 1 mg/kg qd sc - UFH 10,000 units bid, if severe kidney insufficiency</td>
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<td>Lopes [17]</td>
<td>2021</td>
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<td>Brazil</td>
<td>Multicenter</td>
<td>Moderate</td>
<td>310/304</td>
<td>Therapeutic dose - Rivaroxaban 15–20 mg qd po - Enoxaparin 1 mg/kg bid or UFH, target for aPTT 1.5–2.5 times the mean normal level or anti-Xa levels (0.3–0.7 IU/ml) if clinically unstable patients</td>
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<td>Perepu [18]</td>
<td>2021</td>
<td>RCT</td>
<td>US</td>
<td>Multicenter</td>
<td>Severe</td>
<td>87/86</td>
<td>Intermediate dose - Enoxaparin 1 mg/kg qd sc</td>
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<tr>
<td>Helms [21]</td>
<td>2021</td>
<td>Retrospective cohort study</td>
<td>France</td>
<td>Multicenter</td>
<td>Severe</td>
<td>71/108</td>
<td>Therapeutic dose - LMWH 100 IU/kg bid sc, not exceeding 10,000 IU/12 hr - UFH 500 IU/kg qd, if creatinine clearance &lt;30 ml/min</td>
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<td>Taccone [24]</td>
<td>2020</td>
<td>Retrospective cohort study</td>
<td>Belgium</td>
<td>Single center</td>
<td>Severe</td>
<td>18/22</td>
<td>Therapeutic dose - Enoxaparin 4,000 IU bid sc - UFH 1,500–2,200 IU/hr continuous infusion, in case of RRT and/or ECMO</td>
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<td>Lavinio [23]</td>
<td>2021</td>
<td>Retrospective cohort study</td>
<td>UK, Italy, Spain, Belgium, Austria</td>
<td>Multicenter</td>
<td>Severe</td>
<td>274/435</td>
<td>Therapeutic dose - Enoxaparin 50–100 IU/kg bid</td>
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<td>Jonmarker [22]</td>
<td>2020</td>
<td>Retrospective cohort study</td>
<td>Sweden</td>
<td>Single center</td>
<td>Severe</td>
<td>85/67</td>
<td>Therapeutic dose (n=37) - Tinzaparin ≥175 IU/kg or Dalteparin ≥200 IU/kg Intermediate dose (n=48) - Tinzaparin &gt;450 IU but &lt;175 IU/kg or Dalteparin &gt;5,000 IU but &lt;200 IU/kg</td>
</tr>
</tbody>
</table>

RCT: randomized clinical trial; LMWH: low-molecular weight heparin; UFH: unfractionated heparin; aPTT: activated partial thromboplastin time; qd: once a day; sc: subcutaneous; bid: twice a day; po: per oral; RRT: renal replacement therapy; ECMO: extracorporeal membrane oxygenation.
Anticoagulation dosing for COVID-19 patients

DISCUSSION

COVID-19 pneumonia is associated with a hypercoagulable condition caused by endothelial disturbance and an intense prothrombotic inflammatory response [25], which results in pulmonary microvascular thrombosis linked to poor outcomes [26,27]. In a situation where the importance of anticoagulation is emerging, this meta-analysis of previous RCT studies found no significant difference in mortality [15,17] between the group using an anticoagulant as a therapeutic dose and a group using an anticoagulant as a prophylactic dose in moderate- severity patients admitted due to COVID-19. Although the incidence of thrombosis was significantly lower in the anticoagulant-treated group, the frequency of major bleeding in the above two studies was significantly higher in the therapeutic group than in the prophylactic group. Sixteen fewer patients in the prophylactic group (1,350 patients) developed thrombosis than in the treated group (1,490 patients). In the treated group (1,490 patients), the frequency of thrombosis was less than in the prophylactic dose group (1,350 patients), but there were 19 more patients with major bleeding events in the treated group. Since anticoagulant treatment can be accompanied by bleed-
ing, both the frequency of thrombosis and bleeding must be considered when evaluating the clinical benefits. Therefore, it seems that there was no clinical benefit of therapeutic dose of anticoagulation to hospitalized patients with moderate-severe COVID-19. In addition, no significant difference in the progression of organ failure was observed according to the dosage of anticoagulants.

There was no significant difference in mortality in the RCT studies in this analysis between patients with COVID-19 given an anticoagulant as a therapeutic or intermediate dose and those given a prophylactic dose of anticoagulant. In two previous RCTs [18,19], the incidence of thrombosis in the therapeutic group (50 out of 617 patients) and the prophylactic group (71 out of 645 patients) was lower in the therapeutic group, whereas major bleeding was more common in the therapeutic group by seven patients. In the meta-analysis, no significant difference was observed between the two groups in thrombus formation and bleeding. In critically ill COVID-19 patients, therapeutic anticoagulant administration did not appear to have significant benefits.
Based on these results, the risk of bleeding was evaluated, and it seems possible to selectively apply a therapeutic dose of anticoagulant treatment for DVT prophylaxis to the low-risk COVID-19 patient group. Heparin, which exerts anti-inflammatory and antiviral effects, is preferred over mechanical methods worn on the lower extremities (compression stockings or intermittent air compression devices) for thrombosis prevention therapy in patients hospitalized for COVID-19. A previous study found no difference in the antithrombotic effect of administering low-dose unfractionated heparin two or three times a day [28]. Although low-molecular-weight heparin has the advantage of being administered once a day, the thrombotic prevention effect is almost the same as that of a prophylactic dose of unfractionated heparin, but the risk of bleeding is lower [29-31].

Oral anticoagulants can be directly used at low doses for thrombosis prevention in patients hospitalized for internal medical conditions. A previous study reported that the bleeding frequency was higher than that of low-molecular-weight heparin administered prophylactically [32], and in patients
with high D-dimer values. Another study found that the thrombotic prevention effect was similar to that of prophylactic low-molecular-weight heparin administration without increasing the frequency of bleeding [33]. Oral Factor Xa therapy is not preferred over prophylaxis with low-molecular-weight heparin because of its high bleeding rate, but it can be considered when low-molecular-weight heparin cannot be used. Considering the risk of bleeding [34], if the risk of bleeding is judged to be low, heparin therapy may be selected.

According to the International Society on Thrombosis and Haemostasis (ISTH), low-molecular-weight heparin is recommended first after careful evaluation of the side effects related to using the drug, and it is needed to evaluate bleeding risk as a universal strategy for routine thrombosis prevention using standard-dose unfractionated heparin or low-molecular-weight heparin in COVID-19 patients admitted to general wards other than ICUs [35,36]. In a minority opinion, mid-dose low-molecular-weight heparin could also be considered [35,36].

ISTH recommends a prophylactic dose of unfractionated heparin or low-molecular-weight heparin for COVID-19 patients admitted to ICUs after the careful assessment of bleeding risk [16,18,35]. In patients at high risk for thrombosis, the use of medium-dose low-molecular-weight heparin may be considered. Therapeutic doses of heparin should not be considered for DVT prophylaxis until the results of RCTs are available. Thrombosis prevention using mechanical methods (i.e., intermittent air compression devices) in addition to drug therapy should also be considered [36].

The guidelines of the American Society of Hematology make conditional recommendations regarding the use of therapeutic or intermediate anticoagulants in patients with COVID-19 without thrombosis, but the level of evidence is low [37]. These recommendations were issued prior to the release of important RCT results and may be revised in the future. The National Institute of Health does not recommend an anticoagulant for prophylactic anticoagulation therapy in COVID-19 patients [38]. However, these guidelines were issued prior to the release of important RCT results and may be revised in the future.

This review had some limitations. First, we did not perform subgroup analysis according to known risk factors such as age, body mass index, and underlying comorbidities. Even if COVID-19 patients are hospitalized in a general ward, there would be differences in thromboembolic risks depending upon individual medical history, including bedridden or ambulatory status. Second, several retrospective cohort studies and trial-level data were included. However, most of the patients were those included in RCTs rather than cohort studies, and we showed the results of both RCTs and cohort studies. Third, the anticoagulation drug type and dosage were different

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Table 2. Summary of findings and grading quality of the evidence

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study design</th>
<th>Anticipated absolute effect (95% CI)</th>
<th>Relative risk (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>28-Day, 30-day, ICU, or in-hospital mortality</td>
<td>RCT</td>
<td>194 Per 1,000 200 Per 1,000 (177–225)</td>
<td>1.03 (0.91–1.16)</td>
<td>4,673 (5)</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Cohort study</td>
<td>263 Per 1,000 166 Per 1,000 (13–263)</td>
<td>0.63 (0.39–1.00)</td>
<td>331 (2)</td>
<td>Very low</td>
</tr>
<tr>
<td>Lavinio et al. [23] reported therapeutic dose of anticoagulants was associated with significant reduction in ICU mortality compared to prophylactic dose (log odds, 0.64; 95% CI, 0.18–1.1; P=0.0069).</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thromboembolic event</td>
<td>RCT</td>
<td>59 Per 1,000 42 Per 1,000 (33–55)</td>
<td>0.72 (0.56–0.93)</td>
<td>4,664 (5)</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Cohort study</td>
<td>207 Per 1,000 139 Per 1,000 (70–273)</td>
<td>0.67 (0.34–1.32)</td>
<td>1,043 (4)</td>
<td>Very low</td>
</tr>
<tr>
<td>Bleeding</td>
<td>RCT</td>
<td>14 Per 1,000 26 Per 1,000 (17–40)</td>
<td>1.88 (1.23–2.87)</td>
<td>4,667 (5)</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Cohort study</td>
<td>52 Per 1,000 40 Per 1,000 (22–72)</td>
<td>0.69 (0.38–1.25)</td>
<td>1,040 (3)</td>
<td>Very low</td>
</tr>
</tbody>
</table>

CI: confidence interval; GRADE: Grading of Recommendations Assessment Development and Evaluation; ICU: intensive care unit; RCT: randomized clinical trial.

a) One study has heterogeneity regarding anticoagulants dose; b) Overall serious risk of bias across studies; c) Imprecision due to limited sample size; d) Very few events in both intervention and control group.
in each study. However, we did not control for confounding variables, which could affect bleeding risks. Recommendations should be changed based on new evidence. We have been updated our recommendations periodically by living guideline development scheme for including new published studies (last update was done in May 2022). And we are also monitoring other countries or institutions’ recent recommendations [39].

In conclusion, there was no significant difference in mortality in the RCT studies between hospitalized patients (in the general ward or ICU) with COVID-19 given an anticoagulant as a therapeutic or intermediate dose and those given an anticoagulant as a prophylactic dose. In patients with moderate COVID-19, thromboembolic events were less common at the therapeutic or intermediate dose, but bleeding events was significantly higher. The incidence of thromboembolic and bleeding events was not statistically significant in the group of patients with severe COVID-19 in the RCTs. Therefore, prophylactic doses of anticoagulants is recommended for both groups. Future studies are needed to determine more individualized anticoagulation guidance for all COVID-19 patients.

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

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ORCID
Hyeon-Jeong Lee https://orcid.org/0000-0002-0822-2420
Hye Jin Jang https://orcid.org/0000-0003-4637-5564
Won-Il Choi https://orcid.org/0000-0001-7705-0098
Joonsung Joh https://orcid.org/0000-0002-5044-2742
Junghyun Kim https://orcid.org/0000-0002-6868-6534
Jungeun Park https://orcid.org/0000-0002-1129-5495
Miyoung Choi https://orcid.org/0000-0002-2424-9965

AUTHOR CONTRIBUTIONS
Conceptualization: HJL, HIJ, MC. Methodology: MC. Formal analysis: HJL, HIJ, JK. Data curation: HJL, HIJ, WC, JJ. Visualization: JP. Project administration: MC, JP. Funding acquisition: MC. Writing–original draft: HJL, HIJ. Writing–review & editing: MC, WC, JJ, JK, JP.

SUPPLEMENTARY MATERIALS
Supplementary materials can be found via https://doi.org/10.4266/acc.2022.0142.

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Background: The role of positive pressure ventilation, central venous pressure (CVP) and inflammation on the occurrence of acute kidney injury (AKI) have been poorly described in mechanically ventilated patients secondary to coronavirus disease 2019 (COVID-19).

Methods: This was a monocenter retrospective cohort study of consecutive ventilated COVID-19 patients admitted in a French surgical intensive care unit between March 2020 and July 2020. Worsening renal function (WRF) was defined as development of a new AKI or a persistent AKI during the 5 days after mechanical ventilation initiation. We studied the association between WRF and ventilatory parameters including positive end-expiratory pressure (PEEP), CVP, and leukocytes count.

Results: Fifty-seven patients were included, 12 (21%) presented WRF. Daily PEEP, 5 days mean PEEP and daily CVP values were not associated with occurrence of WRF. 5 days mean CVP was higher in the WRF group compared to patients without WRF (median [IQR], 12 mm Hg [11-13] vs. 10 mm Hg [9–12]; P=0.03). Multivariate models with adjustment on leukocytes and Simplified Acute Physiology Score (SAPS) II confirmed the association between CVP value and risk of WRF (odd ratio, 1.97; 95% confidence interval, 1.12–4.33). Leukocytes count was also associated with occurrence of WRF in the WRF group (14 G/L [11–18]) and the no-WRF group (9 G/L [8–11]) (P=0.002).

Conclusions: In mechanically ventilated COVID-19 patients, PEEP levels did not appear to influence occurrence of WRF. High CVP levels and leukocytes count are associated with risk of WRF.

Key Words: acute kidney injury; central venous pressure; COVID-19; inflammation; positive end-expiratory pressure

INTRODUCTION

Acute kidney injury (AKI) is a frequent complication among hospitalized patient with coronavirus disease 2019 (COVID-19) [1], with a wide range of incidence reported since the begin-
ning of the epidemic, from 0.5% [2] to 36.6% [3]. Recently, a systematic review estimated the incidence around 10% among patient hospitalized for COVID-19 [4]. In critically ill patients, the incidence of AKI has been reported between 26% and 56% [4-6] and may be associated with severe complications such as the use of renal replacement therapy [7], progression of chronic kidney disease [8], and a higher rate of hospital mortality [9,10].

Pathophysiology of AKI in patients hospitalized in intensive care unit (ICU) for COVID 19 acute respiratory distress syndrome (ARDS) is multifactorial. Virus may exert a direct role on the renal parenchyma, by infecting the cells that express angiotensin-converting enzyme 2 (ACE-2) receptors [11] (podocytes and proximal tubular cells [12]). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes an increase in ACE activity and an overproduction of angiotensin II, leading to a proinflammatory state damaging the kidney [13]. It can also have an effect on glomerular cells [14], with collapsing glomerulopathy [15]. In addition, COVID-19 can lead to elevated levels of inflammatory cytokines, which can cause endothelial dysfunction, microvascular thrombosis and tubular cells damages [16]. Besides, hemodynamic consequences of ventilatory support (i.e., mechanical ventilation with positive pressure) could also directly impact glomerular function. Positive pressure ventilation has been shown to decreases renal blood flow, glomerular filtration rate, urine output, excretion of creatinine and sodium [17,18]. Previous studies has shown that elevated central venous pressure (CVP) is associated with AKI occurrence in ICU, especially in septic shock patients [19,20], suggesting a crucial role of the venous congestion in the development of AKI. By increasing intra thoracic and CVP, positive end-expiratory pressure (PEEP) level could have a direct impact on renal perfusion and occurrence of AKI [21].

The objective of the study was to investigate the relationship between hemodynamics, ventilatory parameters and systemic inflammation, and the progression of AKI in COVID-19 patients who required mechanical ventilation.

MATERIALS AND METHODS

Study Design
We conducted a single center, retrospective cohort study in a 43 beds ICU in France during the COVID-19 surge. This study was approved by Institutional Review Board of Paris 7 University (No. 00006477, HUPNVS). Informed consent was waived by the board.

Patient Population
All patients admitted in ICU from March 2020 to July 2020 for a SARS-CoV-2 pneumonia were screened. SARS-CoV-2 pneumonia was defined by the association of evocative lung lesions seen in computed tomography scan or thoracic radiography and a positive polymerase chain reaction result for SARS-CoV-2. Patients were included if they were 18 years old or older and if they required mechanical ventilation for respiratory support during ICU stay. Patients were excluded if they were mechanically ventilated for another reason than respiratory failure, and if another diagnosis than SARS-CoV-2 was possible to explain the lung injury. Patients were also excluded if they had an AKI due to another disease than SARS-CoV-2 pneumonia during the 3 days before admission to ICU.

Data Collection
Collected data were extracted from electronic and paper medical records. Day 1 was defined as the first day of mechanical ventilation. Demographic data included age, sex, comorbidities, treatment by renin angiotensin inhibitor, immunosuppressive therapy, use of corticosteroids, antiplatelet drug or anticoagulant therapy. Charlson comorbidity index, Simplified Acute Physiology Score (SAPS) II and Sequential Organ Failure Assessment (SOFA) scores [22,23] were calculated 24 hours after admission in ICU. Biological parameters included serum creatinine, urea, leucocytes count, neutrophils count, lymphocytes count, oxygen partial pressure in arterial blood.

Ventilatory and hemodynamic parameters included PEEP, plateau pressure, tidal volume, fraction of inspired oxygen and CVP and correspond to the mean values of the day (4-6 measurements every day for each parameter). According to local nursing monitoring protocols, plateau pressure reported in the medical records were the values of pressure displayed by
the ventilator after a 5 seconds inspiratory pause. Criteria for ARDS were evaluated according to Berlin consensus [24]. Diuresis and daily fluid balance measured every day at the same hour were collected.

**Patient Management**

All patients were managed according to local protocol based on international guidelines. Respiratory management included limitation of tidal volume to 6 ml/kg, limitation of plateau and driving pressure, use of neuromuscular blockade and prone positioning session of at least 16 hours if necessary. PEEP levels were individualized according to a local protocol to improve oxygenation without deteriorating compliance and cardiac output. Patent foramen ovale and pleural effusions were systematically looked for and considered for drainage.

Hemodynamics optimizations were performed using cardiac output monitors for all patients, principally esophageal Doppler. Central line in the superior venous territory and arterial lines were inserted in all patients. CVP was measured continuously.

**Definitions**

The diagnosis of AKI was based on the Kidney Disease Improving Global Outcome (KDIGO) classification [25]. Severe AKI at admission was defined as an increase in serum creatinine level ≥2 times from baseline or ≥353.6 µmol/L or initiation of RRT corresponding to KDIGO stage 2 and 3. Baseline serum creatinine levels were measured in blood samples taken before hospital admission when available. When baseline creatinine was not available, the lowest serum creatinine level measured during the patient’s hospital stay was used if the glomerular filtration rate calculated with Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was ≥75 mL/min/1.73 m². In other cases, the baseline creatinine level was estimated by using the modification of diet in renal disease equation with the assumption of an age-adjusted glomerular filtration rate because this approach performed best in terms of generating the smallest number of false negatives [26].

**New, persistent and transient AKI**

New severe AKI was defined as an increase in serum creatinine level ≥2 times from baseline or ≥353.6 µmol/L or initiation of RRT after 24 hours from inclusion in patients who had no severe AKI upon the initiation of mechanical ventilation (MV). Persistent severe AKI was defined as a steady or increase in KDIGO classification stage between the first 24 hours following initiation of MV and day 5 in patients with KDIGO stage ≥2 at inclusion or between the first 24 hours following initiation of MV and the last day of MV depending on which one comes first. Transient severe AKI was defined as a resolution or a downstaging of AKI between the first 24 hours following inclusion and day 5 (example from KDIGO stage 2 to KDIGO stage 1).

**Worsening renal function**

Worsening renal function (WRF) was defined as a new or persistent severe AKI (WRF+). Patients with no AKI or transient severe AKI were considered as patient without WRF (WRF–).

**Primary endpoint**

The primary endpoint of the study was to investigate the relationship between PEEP, CVP and WRF during the 5 days following the initiation of mechanical ventilation.

**Secondary endpoints**

The secondary endpoint was to identify other risk factors associated with WRF.

**Statistical Analysis**

Quantitative parameters are reported as median with interquartile range (IQR) and qualitative parameters are expressed as number and percentage. Categorical variables were compared using Fisher exact test as appropriate. Continuous variables were compared using Mann-Whitney U-test.

Actualized mean PEEP was defined by the cumulative mean PEEP dose, i.e., the mean PEEP between the day studied and the previous day. We also calculated mean values during 5 days for the daily PEEP, CVP, leukocytes count, and neutrophils count to reflect the overall exposition of the kidney, to elevated pressures and inflammation during the first days of mechanical ventilation.

We developed two multivariable models with adjustment for confounding factors (SAPS II and mean leukocytes count for 5 days) to assess the association between mean CVP level for 5 days, mean PEEP level for 5 days and the risk of WRF. Predicted probabilities of WRF by the models were plotted together with significantly associated variables and a local polynomial regression fitting was performed to visually assess the relationship between the variable and the risk of WRF.

Finally, the relationship between PEEP level and CVP was explored using linear regression. A P-value lower than 0.05 has been considered significant. Odds ratio are reported with 95%
confidence intervals (CIs). All statistical analyses were performed using R statistical software version 4.0.2 (R Core Team, 2020, R Foundation for Statistical Computing; https://www.R-project.org).

RESULTS

Baseline Characteristics
Seventy-three patients with SARS-CoV-2 pneumoniae were screened. Among them, 57 were mechanically ventilated and included in the study. All patients fulfilled Berlin criteria for ARDS. Flowchart is shown in Supplementary Figure 1.

Among the 57 included patients severe AKI was diagnosed in 16 patients (28%). Severe AKI was diagnosed at the time of intubation in 11 patients (19.3%). Among them, four patients presented a transient AKI, and seven patients had a persistent severe AKI. Forty-six patients (80.7%) had no severe AKI at the time of intubation, five developed a new severe AKI. Therefore, 12 patients were included in the WRF+ and 45 patients were included in the WRF– group.

Table 1. Demographic characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>WRF–</th>
<th>WRF+</th>
<th>Total</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>45</td>
<td>12</td>
<td>57</td>
<td>-</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>60 (54–66)</td>
<td>64 (53–70)</td>
<td>62 (54–67)</td>
<td>0.35</td>
</tr>
<tr>
<td>Male</td>
<td>41 (91.1)</td>
<td>7 (58.3)</td>
<td>48 (84.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td>17 (38.6)</td>
<td>10 (83.3)</td>
<td>27 (47.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>Diabetes</td>
<td>17 (38.6)</td>
<td>6 (50.0)</td>
<td>23 (40.4)</td>
<td>0.70</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>3 (7)</td>
<td>0</td>
<td>3 (5.3)</td>
<td>0.57</td>
</tr>
<tr>
<td>Chronic cardiovascular disease</td>
<td>7 (15.9)</td>
<td>2 (18.2)</td>
<td>9 (15.8)</td>
<td>1.00</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>9 (20.9)</td>
<td>3 (27.3)</td>
<td>12 (21.1)</td>
<td>1.00</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>4 (9.3)</td>
<td>5 (45.5)</td>
<td>9 (15.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>Renin–angiotensin–aldosterone system inhibitor therapy</td>
<td>13 (29.5)</td>
<td>8 (72.7)</td>
<td>21 (36.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>Corticosteroid therapy</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td>1 (2.3)</td>
<td>2 (18.2)</td>
<td>3 (5.3)</td>
<td>0.18</td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td>9 (20.5)</td>
<td>2 (18.2)</td>
<td>11 (19.3)</td>
<td>1.00</td>
</tr>
<tr>
<td>Anticoagulant therapy</td>
<td>0</td>
<td>1 (9.1)</td>
<td>1 (1.8)</td>
<td>0.44</td>
</tr>
<tr>
<td>SAPS II at admission</td>
<td>41 (31–49)</td>
<td>52 (46–63)</td>
<td>42 (33–53)</td>
<td>0.05</td>
</tr>
<tr>
<td>SOFA score at admission</td>
<td>7 (5–9)</td>
<td>11 (10–13)</td>
<td>7 (6–10)</td>
<td>0.001</td>
</tr>
<tr>
<td>Charlson comorbidity index</td>
<td>2 (1–3)</td>
<td>3 (2–4)</td>
<td>2 (1–4)</td>
<td>0.12</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>86 (64–109)</td>
<td>227 (102–335)</td>
<td>89 (69–129)</td>
<td>0.001</td>
</tr>
<tr>
<td>Urea (mmol/L)</td>
<td>6.2 (4.4–9.8)</td>
<td>17.3 (9.6–20.6)</td>
<td>6.9 (4.8–12)</td>
<td>0.003</td>
</tr>
<tr>
<td>Leukocytes (G/L)</td>
<td>9 (7–11)</td>
<td>12 (11–15)</td>
<td>10 (7–12)</td>
<td>0.01</td>
</tr>
<tr>
<td>Neutrophils (G/L)</td>
<td>7 (6–10)</td>
<td>11 (10–12)</td>
<td>8 (6–10)</td>
<td>0.01</td>
</tr>
<tr>
<td>Lymphocytes (G/L)</td>
<td>0.8 (0.6–1.1)</td>
<td>1.2 (0.6–1.3)</td>
<td>0.9 (0.6–1.0)</td>
<td>0.33</td>
</tr>
<tr>
<td>Use of vasopressors</td>
<td>30 (68.2)</td>
<td>11 (91.7)</td>
<td>41 (71.9)</td>
<td>0.20</td>
</tr>
<tr>
<td>CVP (mm Hg)</td>
<td>9 (7–11)</td>
<td>11 (10–12)</td>
<td>10 (7–12)</td>
<td>0.01</td>
</tr>
<tr>
<td>PEEP (cm H₂O)</td>
<td>8 (8–10)</td>
<td>9 (8–12)</td>
<td>8 (8–10)</td>
<td>0.21</td>
</tr>
<tr>
<td>P/F ratio</td>
<td>121 (70–223)</td>
<td>108 (84–166)</td>
<td>117 (71–194)</td>
<td>0.59</td>
</tr>
<tr>
<td>Compliance (ml/cm H₂O)</td>
<td>28 (25–37)</td>
<td>34 (28–37)</td>
<td>30 (25–37)</td>
<td>0.32</td>
</tr>
<tr>
<td>Plateau pressure (cm H₂O)</td>
<td>24 (22–26)</td>
<td>25 (23–26)</td>
<td>24 (22–26)</td>
<td>0.64</td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range) or number (%). WRF: worsening renal function; WRF–: patients without WRF; WRF+: patients with a new or persistent severe acute kidney injury; SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment; CVP: central venous pressure; PEEP: positive end expiratory pressure; P/F ratio: ratio between the partial pressure in O₂ and the inspiratory fraction of O₂.
fraction of $O_2$ (P/F ratio), PEEP, compliance, Pplat and inspiratory fraction of oxygen between groups. The CVP was also not different between groups at the time of intubation.

Concerning the need for vasopressors, there was no difference in terms of the number of patients requiring vasopressors between the WRF– and WRF+ group (35 [81.4%] vs. 12 [100.0%], $P=0.249$). There was also no difference in terms of the vasopressors free days during the 5 days post intubation between the WRF– and WRF+ groups (median [IQR], 2 [0–4] vs. 1 [0–2]; $P=0.13$).

**Association between AKI and Ventilatory Parameters**

During the 5 days following the initiation of mechanical ventilation, there was no difference in daily compliance, daily PEEP and daily actualized mean PEEP between groups except for PEEP and actualized mean PEEP at day 2 (Figure 1, Supplementary Figures 2 and 3). The PEEP mean value during the 5 days was not different between the WRF+ and WRF– groups (median [IQR], 10 [9–11] vs. 8 [8–11]; $P=0.09$) (Table 2). The absence of association between PEEP and WRF persisted after multivariable analysis (Supplementary Table 1, Supplementary Figure 4).

**Association between Ventilatory Parameters, CVP and AKI**

The daily values of CVP were not different between the two groups (Supplementary Figure 5). However, the mean value of CVP within 5 days after intubation was more elevated in the WRF+ group than in the WRF–group (median [IQR], 12 [11–13] vs. 10 [9–12]; $P=0.03$) (Table 2). Using multivariable analysis, there was a positive relationship between mean values of CVP during the 5 days and the risk of WRF, with an odd ratio for WRF of 1.97 (95% CI, 1.12–4.33) per increase of 1 mm Hg of CVP (Supplementary Table 2), and a significant increase in risk

![Figure 1](https://www.accjournal.org)
of WRF with CVP values above 10 mm Hg (Figure 2). Investigating the relationship between PEEP and venous pressure, there was a linear relationship between PEEP level and CVP

<table>
<thead>
<tr>
<th>Variable</th>
<th>WRF-</th>
<th>WRF+</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>45</td>
<td>12</td>
<td>-</td>
</tr>
<tr>
<td>Mean PEEP (cm H₂O)</td>
<td>8 (8–11)</td>
<td>10 (9–11)</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean P/F ratio</td>
<td>200 (155–246)</td>
<td>238 (167–257)</td>
<td>0.42</td>
</tr>
<tr>
<td>Mean CVP (mm Hg)</td>
<td>10 (9–12)</td>
<td>12 (11–13)</td>
<td>0.03</td>
</tr>
<tr>
<td>Mean leukocytes (G/L)</td>
<td>9 (8–11)</td>
<td>14 (11–18)</td>
<td>0.002</td>
</tr>
<tr>
<td>Mean neutrophils (G/L)</td>
<td>8 (6–9)</td>
<td>11 (10–15)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range).

PEEP: positive end expiratory pressure; P/F ratio: ratio between the partial pressure in O₂ and the inspiratory; CVP: central venous pressure; WRF: worsening renal function; WRF-: patients without WRF; WRF+: patients with a new or persistent severe acute kidney injury.

**Table 2.** Mean values of PEEP, P/F ratio, CVP, leukocytes, and neutrophils during the 5 days following intubation

**Association between AKI and Biological Parameters**

Daily leukocytes and neutrophils were more elevated in the WRF+ group (Figure 4, Supplementary Figure 6), except for neutrophils on the day 4. The mean value of leukocytes on the 5 days after intubation were 14 G/L (IQR, 11–18) in the WRF+ group and 9 G/L (IQR, 8–11) in the WRF- group (P=0.002), and mean value of neutrophils were also higher in the WRF+ group (11 G/L [IQR, 10–15]) than in the WRF- group (8 G/L [IQR, 6–9]) (P=0.001). We did not observe any difference in lymphocytes count between the two groups (Supplementary Figure 7).

**DISCUSSION**

In the present study, we found no association between PEEP levels and WRF. CVP levels are associated with the risk of WRF.
especially above 10 mm Hg. PEEP may be associated with WRF through its impact on CVP. Inflammation also seems to be a contributor to WRF. The relationship between PEEP and AKI has been evoked multiple times in the literature [27-30]. Anyway, few studies investigated the impact of PEEP levels on occurrence or persistence of AKI to date. The COVID-19 pandemic recently emphasized the major importance of adequate ventilator management of ARDS patients. We showed that PEEP has a dramatic impact on global hemodynamics and may reduce oxygen delivery while improving P/F ratio [31].

The contribution of right side pressure, i.e. CVP, to AKI has been well described [19,20]. A strength of our study is to investigate together PEEP and CVP impact on AKI. The global impact of PEEP on CVP is uncertain [32-34] and relies on various factors (hypovolemia, compliance, right heart function, etc.). It has been proven that PEEP increases CVP, although it is impossible to predict the raise in patients with altered lung compliance. It is therefore consistent with physiology and physiological studies to find an elevation of the PVC level with PEEP level. In our study, CVP levels increases with peep levels, but PEEP levels did not differ between patient with or without WRF. Consistently with literature [21], we found an increased risk of WRF with high values of CVP (above 10 mm Hg). These results highlight the fact that PEEP may contribute to occurrence of WRF through its impact on CVP. Therefore, ventilatory and hemodynamic management of COVID-19 ARDS patients should focus on the evolution of CVP in order to prevent kidney injury. Interestingly, we found that inflammation was a risk factor of WRF. One study has recently found that high neutrophils count in ICU was associated with severe AKI [35].

Our results support the hypothesis of a role of inflammation in case of AKI in COVID 19. Thus, management of the inflam-
The inflammatory part of AKI relies on the control of the disease and may respond to immunomodulatory treatments that were recently put under the light with the pandemic.

In the present study, we decided to consider both new AKI and persistent AKI together. This concept of WRF fits well with ICU daily practice. Indeed, a large proportion of AKI occurs before ICU admission [36]. It seems adequate to consider that the same factors contribute to both development and persistence of AKI.

Our study suffers several limitations. First, the retrospective, single center, nature of our study may prevent us generalizing our results. However, our center is expert in hemodynamic monitoring, with a trained and experienced team, implying that the CVP values reported can be considered reliable. More, all the patients were treated homogeneously, with local protocols in accordance with international guidelines [37].

Second, there were several imbalances between the two groups, and not every variables were taken into account in the analyses, likely due to the limited number of patients. Third, the CVP levels reported were relatively low. This can be explained by the fact that our teams is concerned about maintaining low CVP, in order to limit the repercussions of subsequent right side heart failure. Last, this study was conducted during the first wave of COVID 19, implying that none of these patients received immunomodulatory therapy such as dexamethasone or tocilizumab. In addition, some of these patients did not immediately benefit from enhanced preventive anticoagulation as recommended now [38].

Based on these results, it appears that kidney protection should be an objective of the ventilatory strategy. In mechani-
Central venous pressure, inflammation, COVID-19


Acute and critically ventilated COVID-19 patients, PEEP level did not appear to influence occurrence of WRF; high CVP levels and leukocytes count are associated with risk of WRF.

CONFLICT OF INTEREST

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

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ORCID

Pierre Basse https://orcid.org/0000-0002-5532-6476
Louis Morisson https://orcid.org/0000-0003-4431-8785
Romain Barthélémy https://orcid.org/0000-0002-6493-4326
Nathan Julian https://orcid.org/0000-0003-4144-7549
Manuel Kindermans https://orcid.org/0009-0006-7733-4211
Magaline Collet https://orcid.org/0000-0002-5821-332X
Benjamin Huot https://orcid.org/0009-0002-5949-524X
Etienne Gayat https://orcid.org/0000-0002-3334-3849
Alexandre Mebazaa https://orcid.org/0000-0001-8715-7753
Benjamin G. Chousterman https://orcid.org/0000-0002-9592-7014

AUTHOR CONTRIBUTIONS

Conceptualization: PB, AM, BGC. Data curation: PB, BGC. Formal analysis: LM, BH. Methodology: EG, AM. Visualization: LM, RB, EG. Writing—original draft: PB, RB, NJ, MK, MC, BGC. Writing—review & editing: PB, BGC.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4266/acc.2022.01494.

REFERENCES


INTRODUCTION

The clinical presentation of coronavirus disease 2019 (COVID-19) ranges from asymptomatic illness to severe acute respiratory distress syndrome (ARDS). Approximately 20%–25% of patients with COVID-19 admitted to the hospital require critical care management. Management of hypoxemia and respiratory failure in these patients has presented new challenges for clinicians.
challenges. The oxygen therapy has included nasal prongs with low-flow oxygen, non-rebreathing mask, bilevel positive airway pressure (BiPAP), high-flow nasal oxygen (HFNO), and mechanical ventilation. An important concern faced by the intensivist was how to predict the need for invasive mechanical ventilation (IMV) and when to initiate ventilation in these patients. During the first wave of the pandemic, there was a drive for early intubation based on data from China due to fears of rapidly progressing hypoxemia, concerns about patient self-inflicted lung injury (P-SILI), and risk of aerosolization when using non-invasive techniques [2]. Reports from various centers regarding the increased morbidity and mortality of the ventilated patients led to scepticism regarding the early intubation protocol. The argument was that the perils of mechanical ventilation such as ventilator-induced lung injury and ventilator-associated pneumonia can lead to poor outcomes [3]. This led to increased use of alternate techniques of oxygenation such as HFNO, which could avoid intubation in some patients. However, the mortality and morbidity are worse in patients who fail the HFNO trial and require intubation [4]. The criteria for definition of early and delayed intubation differ by study. An objective method to identify subjects who are likely to fail to respond to non-invasive oxygen therapy is needed.

Roca and colleagues first published the respiratory rate-oxygenation (ROX) index, which can predict whether a pneumonia patient will fail treatment using high-flow nasal cannula. The authors reported that ROX >4.88 predicted the success of HFNO to prevent intubation [5]. A retrospective cohort study by Patel et al. [6] involved serial measurements of ROX index and showed that any decrease in the index from baseline over a 24-hour period of initiation of HFNO was a strong predictor of intubation. The ROX index has been used as a non-invasive tool in coronavirus disease patients to predict failure of HFNO and need for intubation [7,8]. However, there are no data as to whether the outcomes of mechanical ventilation are affected by timing of intubation based on ROX index in COVID-19.

This retrospective cross-sectional study was designed to observe the appropriate timing of intubation based on ROX index in patients with coronavirus pneumonia admitted to the intensive care unit (ICU). Our primary hypothesis was that early intubation in less than 12 hours of measurement of ROX index less than 4.88 is associated with successful extubation and improved survival.

KEY MESSAGES
- There is need for methods to improve poor outcomes in coronavirus disease 2019 (COVID-19) patients with pneumonia who require mechanical ventilation.
- The respiratory rate-oxygenation (ROX) index can be used as an objective method to determine failure of non-invasive methods of oxygenation and timing of initiation of ventilation.
- In patients with COVID-19 pneumonia, early intubation within 12 hours of ROX index.

MATERIALS AND METHODS
This single-center retrospective cross-sectional study was performed in a 16-bed COVID-19 ICU of a rural tertiary care hospital in Kerala, India. The study sample included all patient 18 years or older with laboratory confirmed COVID-19 who underwent mechanical ventilation in this ICU from April 1, 2021 to July 31, 2021, during the second wave of the pandemic in Kerala. After Institutional Review Board approval (No. MOSC/IEC/566/2021), we obtained a waiver for informed consent due to the retrospective nature of the analysis from medical records. The details were evaluated using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist [9].

Positive infection status was confirmed either by rapid antigen testing or reverse transcriptase polymerase chain reaction of nasal or oropharyngeal swab. Patients referred to our center after intubation from another center and patients who opted for palliative care were excluded from the study. The variables collected were demographic characteristics, comorbidities, ratio of SpO2 to fraction of inspired oxygen (SpO2/FiO2) with respiratory rate (ROX index) every 6 hours from admission until intubation, Acute Physiology and Chronic Health Evaluation (APACHE) II score at admission, Sequential Organ Failure Assessment (SOFA) score at admission and at intubation, duration from proven COVID-19 diagnosis to intubation, day of extubation, duration of ICU and hospital stay, incidence of acute kidney injury, pneumothorax, and survival. The primary objective was successful extubation and survival pattern based on time of intubation.

After collection of demographic and clinical data, the intubated patients were categorized into two groups; the early intubation group was patients intubated within 12 hours of
ROX index <4.88 and the delayed intubation group comprised patients intubated more than 12 hours after ROX index <4.88. Demographics, comorbidities, and outcomes of the two groups were compared. Patients were followed until hospital discharge or death.

Treatment Protocol in the ICU
Patients who were unable to maintain \(\text{SpO}_2\)>90% on non-re-breather mask with 15 L/min of oxygen or non-invasive BiPAP were put on HFNO, which was initiated with a flow rate of 40–60 L/min and fraction of inspired oxygen (\(\text{FiO}_2\)) titrated to maintain >90% \(\text{SpO}_2\). The intubation criteria were: (1) hypoxemic respiratory failure with \(\text{SpO}_2\) <90 % despite receiving the maximal fraction of inspired oxygen by HFNO; (2) hypercapnic respiratory failure accompanied by \(\text{pH}<7.3\); (3) uncontrolled metabolic acidosis with hypotension (systolic blood pressure <90 mm Hg or mean blood pressure <65 mm Hg) despite fluid resuscitation; (4) need for airway protection because of altered mental state or aspiration or cardiopulmonary arrest.

The ROX index was measured every 6 hours in all patients on HFNO. Intubation was conducted according to the general guidelines and discretion of the treating physician. The intubated patients were sedated and paralyzed; prone ventilation was started for 12–16 hours each day until there was improvement in oxygenation. Remdesivir was the preferred antiviral agent. All patients admitted to the ICU received parenteral corticosteroids with either dexamethasone or methylprednisolone. Other drugs were anticoagulation with low-molecular weight heparin, prophylactic/therapeutic antibiotics, stress ulcer prophylaxis, nutritional support, vitamins/antioxidant supplements, and drugs according to underlying comorbidities.

Statistical Analysis
Continuous variables are presented as median and interquartile range (IQR) when data did not follow a normal distribution and as mean and standard deviation if data were normal. Qualitative variables are presented as frequencies and percentages. Fisher’s exact test and Pearson chi-square test were used to compare categorical variables. Variables that were clinically important or statistically significant in the univariate logistic regression were selected for multivariate analysis to isolate the contribution of intubation based on ROX index on successful extubation; the odds ratio was reported as effect estimate. Kaplan-Meier survival analysis was conducted to assess survival pattern based on time of intubation. Statistical significance was defined as \(P<0.05\). Analyses were performed using R software (EZR software) and IBM SPSS ver. 19 (IBM Corp.).

RESULTS
The second wave of COVID19 in Kerala, India was from April 2021 to July 2021. A total of 814 COVID19-positive patients was admitted to our hospital during this period, and 216 patients were admitted to the ICU. Among the critically ill, 70 patients were mechanically ventilated, 10 patients were intubated outside the ICU, one patient was transferred to another hospital, and palliative treatment was chosen for one patient. These patients were excluded from analysis (Figure 1). The final group included 58 patients; 20 patients were intubated within 12 hours of ROX index <4.88 (early intubation group) and 38 patients were intubated 12 hours after ROX index <4.88 (delayed intubation group).

The baseline characteristics of the 58 patients who were intubated in our ICU are listed in Table 1. The mean age of the study population was 56.8±13.7 years and 55.0% were males. Type II diabetes mellitus was present in 48.3% of the patients and 50.0% were hypertensive. One patient had a history of chronic liver disease and one patient had a history of treatment for breast carcinoma. The Charlson Comorbidity Index (CCI), APACHE II score at admission, median SOFA score at admission and intubation, and day of intubation after confirmed coronavirus disease were similar in the two groups. The mean ROX index at initiation of HFNO was 5.41±1.92 (Table 1).

The main outcome was successful extubation. In the group of patients intubated within 12 hours of ROX index <4.88, 88.2 % were extubated compared with only 11.8% of the late group (\(P<0.001\)). In the early intubation group, 91.7% of the patients survived until discharge from the hospital, which was significantly higher than the percentage of the delayed intubation group. Incidence of acute kidney injury was higher in the delayed intubation group, although without statistical significance. The median duration of ICU stay was 9 days (IQR, 5–13 days). The total numbers of days in the ICU and hospital were higher in the early intubation group (Table 2).

Other complications in the patients were shock requiring vasopressors (17.2%), arrhythmias, and myocardial ischemia/infarction (5%), but there was no difference between the two groups. Pneumothorax occurred in two patients in the
Figure 1. Flowchart of patients with confirmed diagnosis of coronavirus disease 2019 (COVID-19) infection. NRBM: non-rebreather mask; HFNO: high-flow nasal oxygen; BiPAP: bilevel positive airway pressure; ROX: respiratory rate-oxygenation.

Table 1. Clinical characteristics of COVID-19 patients who required mechanical ventilation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total (n=58)</th>
<th>Time from ROX &lt;4.88 to intubation</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt;12 hr (n=20)</td>
<td>≥12 hr (n=38)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>57±14</td>
<td>55±14</td>
<td>58±14</td>
</tr>
<tr>
<td>Male (%)</td>
<td>55.0</td>
<td>55.0</td>
<td>55.3</td>
</tr>
<tr>
<td>DM (%)</td>
<td>48.3</td>
<td>50.0</td>
<td>47.4</td>
</tr>
<tr>
<td>HTN (%)</td>
<td>50.0</td>
<td>40.0</td>
<td>55.0</td>
</tr>
<tr>
<td>COPD (%)</td>
<td>3.4</td>
<td>5.0</td>
<td>2.6</td>
</tr>
<tr>
<td>CKD (%)</td>
<td>6.9</td>
<td>5.0</td>
<td>8.0</td>
</tr>
<tr>
<td>CAD</td>
<td>13.8</td>
<td>15.0</td>
<td>13.0</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>2 (1–3)</td>
<td>2 (1–3)</td>
<td>2 (1–3)</td>
</tr>
<tr>
<td>Day of intubation after confirmed COVID-19 infection</td>
<td>9 (3–13)</td>
<td>7 (4–12)</td>
<td>9 (3–13)</td>
</tr>
<tr>
<td>SOFA score at admission</td>
<td>3 (2–4)</td>
<td>3 (2–4)</td>
<td>3 (2–4)</td>
</tr>
<tr>
<td>SOFA score at intubation</td>
<td>4 (4–5)</td>
<td>4 (4–4)</td>
<td>4 (4–5)</td>
</tr>
<tr>
<td>APACHE II score at admission</td>
<td>15.1±3.3</td>
<td>13.8±3.3</td>
<td>16.0±2.5</td>
</tr>
<tr>
<td>ROX index at initiation of HFNO</td>
<td>5.4±1.9</td>
<td>5.3±2.3</td>
<td>5.0±1.5</td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation or median (interquartile range) unless otherwise indicated.

delayed intubation group and in one patient in the early intubation group. Tracheostomy was performed in one patient in the delayed intubation group. Variables of clinical importance were selected for the logistic regression model and comprised age, sex, comorbidities, day of intubation after confirmed COVID-19 infection, and SOFA and APACHE scores. The analysis showed that early intubation within 12 hours of ROX index <4.88 was the only factor associated with successful extubation (P<0.001) (Table 3). Kaplan-Meier survival analysis showed that the median survival time was 14.8 days (95% confidence interval [CI], 12.2–17.4 days) for patients who had early intubation and 9.9 days (95% CI, 6.8–13.1 days) in the delayed intubation group (P=0.001) (Figure 2).

Table 2. Comparison of main outcome variables between early and delayed intubation groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Time from ROX &lt;4.88 to intubation &lt;12 hr (n=20)</th>
<th>≥12 hr (n=38)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extubation (%)</td>
<td>88.2</td>
<td>11.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Survival (%)</td>
<td>91.7</td>
<td>8.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Shock (%)</td>
<td>20.0</td>
<td>10.5</td>
<td>0.061</td>
</tr>
<tr>
<td>AKI (%)</td>
<td>20.0</td>
<td>80.0</td>
<td>0.051</td>
</tr>
<tr>
<td>ICU day</td>
<td>13 (7–16)</td>
<td>6 (4–11)</td>
<td>0.007</td>
</tr>
<tr>
<td>Hospital day</td>
<td>18 (14–28)</td>
<td>10 (5–14)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range) unless otherwise indicated.

ROX: respiratory rate-oxygenation; AKI: acute kidney injury; ICU: intensive care unit.

Table 3. Predictors of extubation in mechanically ventilated COVID-19 patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable model</th>
<th>Multivariable model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Age</td>
<td>0.97 (0.93–1.02)</td>
<td>0.30</td>
</tr>
<tr>
<td>Male</td>
<td>0.98 (0.32–3.01)</td>
<td>0.97</td>
</tr>
<tr>
<td>Day of intubation after confirmed COVID-19 infection</td>
<td>0.96 (0.64–1.04)</td>
<td>0.40</td>
</tr>
<tr>
<td>Early intubation based on ROX index</td>
<td>34.6 (6.59–182.71)</td>
<td>0.00</td>
</tr>
<tr>
<td>CAD</td>
<td>0.33 (0.39–2.98)</td>
<td>0.33</td>
</tr>
<tr>
<td>HTN</td>
<td>0.47 (0.15–1.51)</td>
<td>0.20</td>
</tr>
<tr>
<td>DM</td>
<td>0.37 (0.30–2.84)</td>
<td>0.00</td>
</tr>
<tr>
<td>AKI</td>
<td>0.48 (0.13–1.74)</td>
<td>0.27</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>0.77 (0.27–1.18)</td>
<td>0.24</td>
</tr>
<tr>
<td>APACHE II score at admission</td>
<td>0.52 (0.56–1.05)</td>
<td>0.34</td>
</tr>
<tr>
<td>SOFA score at admission</td>
<td>0.92 (0.66–1.56)</td>
<td>0.69</td>
</tr>
<tr>
<td>SOFA score at intubation</td>
<td>0.29 (0.40–2.85)</td>
<td>0.49</td>
</tr>
</tbody>
</table>


DISCUSSION

Deciding if and when to intubate and mechanically ventilate a patient with COVID-19 pneumonia is a difficult decision and is be based on both disease severity and provider judgment. The clinical presentation of COVID-19 varies from asymptomatic infection to severe respiratory distress, and the timing of...
initiation of IMV may have significant implications for patient outcomes [10]. This retrospective analysis of mechanically ventilated coronavirus disease patients showed that the timing of intubation based on ROX index may improve rates of successful extubation and survival.

The rate of IMV requirement varied in the first and second waves of the COVID-19 pandemic [11]. The proportion of COVID-19 patients who required mechanical ventilation in our study (32%) is similar to those in reports from a large tertiary care center in India [10]. Of the 23.5% patients with COVID-19 who required intensive care management, 30.8% required IMV. In a study from China, of 344 patients in the ICU, 100 (29.1%) required intubation [12]. The mean age (56.8±13.7 years) and sex (males 55.0%) of patients requiring mechanical ventilation in our study population were similar to those of previous studies. The most common comorbidities associated with severe COVID-19 disease in this study were hypertension and diabetes mellitus type II, similar to globally reported trends in severe COVID-19 patients [13,14]. The CCI was 2.16±1.47 in our study population. There was no statistically significant difference in CCI between early and delayed intubation groups in our study. A CCI index less than 5 was associated with higher survival rates in patients in the ICU in previously reported critically ill patients [15] but was not the case in our patient group.

In the present study, the median SOFA score at admission was 3 and SOFA at intubation was 4. Serial evaluation of SOFA scores during ICU admission is a good indicator of prognosis, and an increase in score during the first 48 hours predicts a 50% mortality rate [16,17]. However, in COVID-19 pneumonia, the discriminatory accuracy of SOFA for predicting mortality was poor and significantly inferior to using only age. The median SOFA score was only 6 (IQR, 4–8) in a previous study involving nearly 1,000 intubated COVID-19 patients with 59.3% mortality [18]. Thus, this clinical scoring system might be less accurate in COVID-19 pneumonia patients as such patients have severe single organ dysfunction (hypoxemia) and less variation in SOFA score. APACHE II seems to perform better in predicting severity of COVID-19 [10]. However, in this study, there was no statistically significant difference between the two groups for APACHE II score at admission to an ICU.

The ROX index is a simple scoring system devised to predict the failure of HFNO in acute hypoxemic respiratory failure [5]; it has shown utility in not just predicting intubation in COVID-19, but also the need for hospital admission [19]. Patel et al. [20] studied the utility of the ROX index in predicting the need for IMV in COVID-19 pneumonia patients and found that a score <5 at initiation predicted the need for IMV (odds ratio [OR], 2.137; P=0.052). The mean time to intubation was 2.5 days with 47% mortality in patients requiring IMV. The average ROX index of the patients admitted to our ICU was 5.41±1.92 on initiation of HFNO.

In this study, we classified COVID-19 patients who required IMV in our ICU into two groups: one group was intubated within 12 hours of ROX index <4.88 (early) and the other group was intubated 12 hours or more after ROX index<4.88 (delayed). Successful extubation (88.2%) and higher survival were noted in the early intubation group. These observations are in agreement with multiple studies that showed early intubation after hospital admission in COVID-19 patients to be associated with favorable outcomes [10,21]. The systematic review and meta-analysis of non-randomized cohort studies by Papoutsi et al. [22] showed different results from ours in intubated COVID-19 patients. Those authors concluded that timing of intubation had no effect on mortality or morbidity of such critically ill patients. However, their definitions of early and late were intubation within 24 hours or after 24 hours of ICU admission. This definition was not related to patients’ clinical status and could be the reason for the difference in findings.

The decision to intubate patients with COVID-19 pneumonia is based on multiple factors and varies among centers and clinicians. The standard intubating criteria in acute hypoxemic respiratory failure used in non-COVID-19 patients might not be enough in these patients. Intubating COVID-19 patients early may have several benefits, like prevention of P-SILI due to spontaneous breathing with large tidal volumes and increasing respiratory effort [23]. Therefore, it is important to identify an objective score to predict the need for intubation that can lead to favorable outcomes, and ROX index fits this requirement.

Factors like age, comorbidities, APACHE and SOFA scores, or day of intubation after diagnosis of COVID-19 that can affect extubation and survival in critically ill patients were analyzed along with timing of intubation based on ROX index. Presence of acute kidney injury and hemodynamic compromise were not different in the patients who were successfully extubated. The multiple logistic regression analysis in this study showed the role of early intubation based on ROX index in extubation (Table 3).

The mortality rate (79.3%) in our study population of severe
COVID-19 with IMV was high, and bleak outcomes have been reported in ventilated COVID-19 patients worldwide [24]. This study was performed during the second wave of the pandemic in Kerala, India, which had a higher case fatality rate [25] with more frequent severe ARDS than in the first wave. Early intubation based on ROX index improved survival in our study population as evidenced by Kaplan-Meier survival analysis (Figure 2), and this was not influenced by demographics or comorbidities of the patients.

A limitation of the present study is the small sample size. This was a single-center study performed in a medium-sized hospital that serves a relatively small geographic area. Therefore, our results must be considered with caution. However, in a pandemic, any new information that can change the trajectory of the disease is relevant, and little information is available on an objective measure to decide when to intubate in COVID-19 patients with pneumonia and ARDS. A multi-centric prospective study for the use of ROX index in timing of intubation of these patients may provide robust evidence for a change in practice for treatment of COVID-19 patients.

In pneumonia due to COVID-19, early intubation within 12 hours of ROX index less than 4.88 is associated with improved chances of successful extubation and survival. As ROX index is a simple tool, its use as an objective method to predict failure of HFNO and to decide on IMV in patients with COVID-19 should be encouraged.

CONFLICT OF INTEREST

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

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ORCID

Sara Vergis https://orcid.org/0000-0002-9193-9819
Sam Philip https://orcid.org/0000-0001-9596-4491

Vergis Paul https://orcid.org/0000-0002-0990-2794
Manjit George https://orcid.org/0000-0002-6725-8722
Nevil C Philip https://orcid.org/0000-0001-5682-5026
Mithu Tomy https://orcid.org/0000-0001-8001-9980

AUTHOR CONTRIBUTIONS

Conceptualization: SVK, MG. Methodology: VP, NCP, MT. Data curation: SVK, NCP, NP, MT. Visualization: VP, NCP. Project administration: SP. Writing—original draft: SVK. Writing—review & editing: SVK, VP, MG.

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17. Fuchs PA, Czech IJ, Krzych IJ. Mortality prediction using SOFA score in critically ill surgical and non-surgical patients: which parameter is the most valuable? Medicina (Kaunas) 2020;56:273.
Background: Respiratory quotient (RQ) may be used as a tissue hypoxia marker in various clinical settings but its prognostic significance in patients undergoing extracorporeal cardiopulmonary resuscitation (ECPR) is not known.

Methods: Medical records of adult patients admitted to the intensive care units after ECPR in whom RQ could be calculated from May 2004 to April 2020 were retrospectively reviewed. Patients were divided into good neurologic outcome and poor neurologic outcome groups. Prognostic significance of RQ was compared to other clinical characteristics and markers of tissue hypoxia.

Results: During the study period, 155 patients were eligible for analysis. Of them, 90 (58.1%) had a poor neurologic outcome. The group with poor neurologic outcome had a higher incidence of out-of-hospital cardiac arrest (25.6% vs. 9.2%, P=0.010) and longer cardiopulmonary resuscitation to pump-on time (33.0 vs. 25.2 minutes, P=0.001) than the group with good neurologic outcome. For tissue hypoxia markers, the group with poor neurologic outcome had higher RQ (2.2 vs. 1.7, P=0.021) and lactate levels (8.2 vs. 5.4 mmol/L, P=0.004) than the group with good neurologic outcome. On multivariable analysis, age, cardiopulmonary resuscitation to pump-on time, and lactate levels above 7.1 mmol/L were significant predictors for a poor neurologic outcome but not RQ.

Conclusions: In patients who received ECPR, RQ was not independently associated with poor neurologic outcome.

Key Words: cardiopulmonary resuscitation; extracorporeal membrane oxygenation; hypoxia; lactic acid

INTRODUCTION

The use of extracorporeal cardiopulmonary resuscitation (ECPR), defined as extracorporeal membrane oxygenation (ECMO) implantation during cardiopulmonary resuscitation (CPR)
is increasing. Recent data from the Extracorporeal Life Support Organization Registry have demonstrated a more than 20-fold increase in annual ECPR cases from less than 100 in 2009 to more than 2000 in 2021 [1] and the American Heart Association guideline now gives the recommendation to consider ECPR as an alternative method of CPR for patients with reversible causes of cardiac arrest after more than 10 minutes of conventional CPR [2]. With the increasing use of ECPR, it has become crucial to understand proper management to achieve hemodynamic optimization after ECPR to improve outcomes.

One of the most important goals of CPR including ECPR is to preserve higher cortical function of the brain and many studies have been conducted to investigate if markers of tissue hypoxia are correlated with neurologic outcomes in this patient population [3-5]. An oxygen-derived tissue hypoxia marker: lactate has been associated with neurologic outcomes in these patients. [6]. However, lactate levels can increase with stress response, β-2 adrenergic stimulation, or hepatic dysfunction which suggest that elevated lactate level may not always represent deficiency in tissue oxygen delivery [7]. Thus, CO₂-derived markers such as the venous-arterial difference in CO₂ tension (∆pCO₂) and respiratory quotient (RQ) may be more useful. In hypoxic states, accumulation of proton in tissues may lead to higher CO₂ production due to buffering action of carbonic anhydrase to increase ∆pCO₂. But, there are studies that indicate ∆pCO₂ better represents status of perfusion rather than tissue hypoxia per se [8,9]. In macro- and micro-circulatory failure, RQ can increase through variety of mechanisms including cells converting to anaerobic metabolism to produce the needed energy. The prognostic role of RQ as a CO₂-derived tissue hypoxia marker is relatively well-studied in the sepsis [10,11] and conventional CPR literature [12,13], but the role of RQ in patients with ECPR has not been extensively studied. Thus, this study was performed to investigate whether RQ measured immediately following initiation of ECPR can predict adverse neurologic outcomes in these patients.

**MATERIALS AND METHODS**

**Study Cohort**

All adult patients (age >18 years) who received ECPR and survived for >24 hours between May 1, 2004, and April 30, 2020, at a tertiary referral hospital in Seoul, Korea were included in the study. Patients who transferred from other hospitals, who failed ECMO implantation and who had insufficient data for calculating RQ were excluded.

This study was performed according to the Helsinki Declaration and approved by the Institutional Review Board of Samsung Medical Center (No. 2020-10-084-001). The Institutional Review Board waived the requirement for informed consent because of the observational nature of the research.

**Operation of ECPR**

ECPR was defined as both successful venoarterial ECMO implantation and pump-on with cardiac massage during the index procedure in patients with cardiac arrest. When a return of spontaneous circulation (ROSC) was achieved during ECMO cannulation, ECMO implantation process was not interrupted [14]. Detailed information on the procedure and management of ECPR in our institute has been previously reported [3,15]. In brief, ECPR was considered during cardiac arrest, if the cause of the arrest was presumed to be reversible and the ROSC did not occur despite conventional high-quality CPR performed for more than 10 minutes. ECPR was not performed in patients whose life expectancy was limited to less than 6 months, patients with end-stage malignancies, patients with unwitnessed arrest, patients in whom physical activity was limited, patients in whom the airway was not protected during CPR, or patients in whom CPR was prolonged at the time of initial contact for ECMO implantation (>60 minutes) [3,16].

The intensivists determined the target temperature for targeted temperature management (TTM) according to the hospital’s protocol. The TTM was operated using surface cooling devices. We used either cooling pads or a commercial temperature regulation system consisting of hydrogel pads (Arctic Sun, Medivance Corp.).

**Definitions and Outcomes**

Clinical features, including underlying comorbidities, inten-
Respiratory quotient and poor neurologic outcome

device care unit treatment, and ECPR details, were collected retrospectively by medical record review. All data were collected by a trained study coordinator using a standardized case report form. If the same biological markers were measured several times before ECPR initiation, the value measured at the closest time to ECPR initiation was used.

Arterial and venous blood gas samples collected within a 30-minute interval during the first 24 hours after ECPR initiation were used to calculate RQ. The plasma hemoglobin and lactate levels taken closest to the time of venous blood gas sampling were used to calculate and analyze the RQ. The RQ was calculated as the ratio between the ΔpCO₂ and the arterial-venous difference in O₂ content (Ca-vO₂). Specifically, the calculations were performed as follows: ΔpCO₂=venous CO₂ tension (PvCO₂)−arterial CO₂ tension (PaCO₂); Ca-vO₂=arterial O₂ content (CaO₂)−venous O₂ content (CvO₂); CaO₂=1.34×arterial O₂ saturation (SaO₂)×plasma hemoglobin+0.003×arterial O₂ tension (PaO₂); CvO₂=1.34×venous O₂ saturation (SvO₂)×plasma hemoglobin+0.003×venous O₂ tension (PvO₂) [17]. The time from initiation of chest compressions to the activation time of ECMO pump was defined as CPR to ECMO pump-on time [3,14].

The primary outcome was neurologic status at hospital discharge. Neurologic status was evaluated by the Glasgow-Pittsburgh cerebral performance categories (CPC) scale [18,19]. Good neurologic outcomes were defined as CPC scores of 1 and 2, and poor neurologic outcomes were defined as CPC score of 3, 4, and 5. Patients were graded on the CPC scale by two independent intensivists who reviewed their medical records thoroughly (YIL and JAR). The secondary outcome was the length of hospital stay after ECPR and hospital mortality.

Results

During the study period, 433 patients underwent ECPR and survived over 24 hours. Patients transferred from other hospitals (n=12), unsuccessful ECMO implantation (n=32), and insufficient data for initial RQ calculation (n=234) were excluded. Finally, data from 155 patients who received ECPR were retrieved for analysis (Figure 1).

Baseline Characteristics

Baseline clinical characteristics are presented in Table 1. Ninety patients (58.1%) had poor neurologic outcomes at hospital discharge. The median age of the patients was 60.0 (IQR, 51.0–72.0) years, and 112 (72.3%) were males. Sex, body mass index, site of ECMO implantation, initial shockable rhythm, and the proportion of ROSC were similar in both the groups. The proportion of patients with hypertension (54.4% vs. 33.8%, P=0.011) and coronary artery disease (30.0% vs. 15.4%, P=0.035) was higher in the group with the poor neurologic outcome than in the group with good neurologic outcome. Compared with the good neurologic outcome group, the

Statistical Analysis

Continuous variables are described as mean±standard deviation or medians with interquartile ranges (IQRs) and categorical variables are presented as numbers and percentages. To compare characteristics and clinical outcomes between two groups, we used the chi-square test or Fisher’s exact test for categorical variables, and Student t-test or Wilcoxon rank-sum test for continuous variables. A logistic regression model was used to estimate the odds ratios for poor neurologic outcomes. Clinical variables obtained at baseline ECPR with a P<0.1 in univariate analyses were included in the multiple logistic regression model for poor neurologic outcomes. Odds ratios with 95% confidence intervals (CIs) were also calculated. The discriminatory power of each hypoxia parameter was assessed by the area under each receiver operating characteristic curve (AUROC). Statistical analysis were performed with IBM SPSS version 25.0 for Windows (IBM Corp.) and MedCalc 19.5.2 (MedCalc Software). For all analyses, a two-tailed test with a P<0.05 was considered statistically significant.

Figure 1. Study flow diagram. ECPR: extracorporeal cardiopulmonary resuscitation; ECMO: extracorporeal membrane oxygenation; RQ: respiratory quotient.
Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Good neurologic outcome (n=65)</th>
<th>Poor neurologic outcome (n=90)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>57 (47–65)</td>
<td>67 (52–75)</td>
<td>0.001</td>
</tr>
<tr>
<td>Male</td>
<td>50 (76.9)</td>
<td>62 (68.9)</td>
<td>0.270</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.0 (21.3–27.2)</td>
<td>24.0 (21.5–26.9)</td>
<td>0.745</td>
</tr>
<tr>
<td>Current smoker</td>
<td>19 (29.2)</td>
<td>17 (18.9)</td>
<td>0.142</td>
</tr>
<tr>
<td>Comorbidity (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>19 (29.2)</td>
<td>35 (38.9)</td>
<td>0.213</td>
</tr>
<tr>
<td>Hypertension</td>
<td>22 (33.8)</td>
<td>49 (54.4)</td>
<td>0.011</td>
</tr>
<tr>
<td>Malignancy</td>
<td>8 (12.3)</td>
<td>11 (12.4)</td>
<td>0.992</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>10 (15.4)</td>
<td>27 (30.0)</td>
<td>0.035</td>
</tr>
<tr>
<td>Peripheral arterial occlusive disease</td>
<td>2 (3.1)</td>
<td>6 (6.7)</td>
<td>0.469</td>
</tr>
<tr>
<td>Stroke</td>
<td>4 (6.2)</td>
<td>7 (7.9)</td>
<td>0.761</td>
</tr>
<tr>
<td>History of percutaneous coronary intervention</td>
<td>14 (21.5)</td>
<td>19 (21.3)</td>
<td>0.977</td>
</tr>
<tr>
<td>History of coronary artery bypass graft</td>
<td>2 (3.1)</td>
<td>9 (10.0)</td>
<td>0.121</td>
</tr>
</tbody>
</table>

Characteristics of ECPR

<table>
<thead>
<tr>
<th>Location of ECMO implantation</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive care unit</td>
<td>20 (30.8)</td>
<td>36 (40.0)</td>
<td>0.730</td>
</tr>
<tr>
<td>Catheterization laboratory</td>
<td>27 (41.5)</td>
<td>17 (18.9)</td>
<td></td>
</tr>
<tr>
<td>Emergency room</td>
<td>17 (26.2)</td>
<td>35 (38.9)</td>
<td></td>
</tr>
<tr>
<td>Operation room</td>
<td>1 (1.5)</td>
<td>2 (2.2)</td>
<td></td>
</tr>
<tr>
<td>Out-of-hospital cardiac arrest</td>
<td>6 (9.2)</td>
<td>23 (25.6)</td>
<td>0.010</td>
</tr>
<tr>
<td>Initial shockable rhythm</td>
<td>26 (40.0)</td>
<td>32 (35.6)</td>
<td>0.573</td>
</tr>
<tr>
<td>Defibrillation</td>
<td>34 (52.3)</td>
<td>56 (62.2)</td>
<td>0.217</td>
</tr>
<tr>
<td>ROSC before ECMO implantation</td>
<td>30 (46.9)</td>
<td>35 (38.9)</td>
<td>0.323</td>
</tr>
<tr>
<td>CPR to pump-on time (min)</td>
<td>25.2 (15.0–36.8)</td>
<td>33.0 (24.0–47.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Initial SOFA score(a)</td>
<td>14.0 (11.5–16.0)</td>
<td>15.0 (13.0–17.0)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

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

ECPR: extracorporeal cardiopulmonary resuscitation; ECMO: extracorporeal membrane oxygenation; ROSC: return of spontaneous circulation; CPR: cardiopulmonary resuscitation; SOFA: Sequential Organ Failure Assessment.

\(a\) SOFA score was calculated using worst values within 24 hours from ECPR. Cardiovascular variable was calculated as 4 in all cases.

Poor neurologic outcome group had a higher proportion of out-of-hospital cardiac arrests (25.6% vs. 9.2%, P=0.010) and longer CPR to pump-on time (33.0 vs. 25.2 minutes, P=0.001).

**ECPR Treatment**

Data on ECPR management are presented in Table 2. After ECPR, ECMO duration, rate of TTM, rate of mechanical ventilator, vasopressors, and rate of intraaortic balloon counterpulsation did not differ between the two groups. However, the rate of continuous renal replacement therapy (52.2% vs. 23.1%, P<0.001) was higher in the group with poor neurologic outcomes than in the group with good neurologic outcomes. Most ECMO-related complications, such as stroke, limb ischemia, and bleeding at the ECMO site, did not differ between the two groups, but gastrointestinal bleeding (10.0% vs. 1.5%, P=0.046) occurred more frequently in the group with a poor neurologic outcome than in the group with good neurologic outcome.

**Initial Tissue Hypoxia Parameters and Clinical Outcomes**

The number of patients in the two groups according to the distribution of the initial RQ are presented in Figure 2. The median initial RQ of all patients was 2.0 (IQR, 1.4–3.0) (Table 3). The median initial RQ was 2.2 (IQR, 1.5–3.6) in the poor outcome group and 1.7 (IQR, 1.1–2.8) in the good outcome group (P=0.021). In all patients, the median ΔpCO₂ was 8.5 mm Hg (IQR, 5.0–14.1 mm Hg), and the median serum lactate level was 7.0 mmol/L (IQR, 3.6–11.7 mmol/L). The median serum lactate level (8.2 vs. 5.4 mmol/L, P=0.004) was elevated in the poor neurologic outcome group than in the good neurologic outcome group; however, the ΔpCO₂ value (9.7 vs. 7.0 mm Hg, P=0.093) was similar between the two groups. Patients with poor neurologic outcomes had significantly higher in-hospital...
Respiratory quotient and poor neurologic outcome

Table 2. ECPR treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Good neurologic outcome (n=65)</th>
<th>Poor neurologic outcome (n=90)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-ECPR management</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECMO duration (hr)</td>
<td>63.7 (34.6–119.8)</td>
<td>60.6 (25.0–130.1)</td>
<td>0.776</td>
</tr>
<tr>
<td>Targeted temperature management</td>
<td>14 (21.5)</td>
<td>19 (21.1)</td>
<td>0.949</td>
</tr>
<tr>
<td>Mechanical ventilator</td>
<td>52 (80.0)</td>
<td>75 (83.3)</td>
<td>0.595</td>
</tr>
<tr>
<td>CRRT</td>
<td>15 (23.1)</td>
<td>47 (52.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vasopressor</td>
<td>62 (95.4)</td>
<td>82 (91.1)</td>
<td>0.360</td>
</tr>
<tr>
<td>Intra-aortic balloon counter pulsation</td>
<td>6 (9.2)</td>
<td>6 (6.7)</td>
<td>0.556</td>
</tr>
<tr>
<td>Left ventricle venting</td>
<td>2 (3.1)</td>
<td>5 (5.6)</td>
<td>0.700</td>
</tr>
<tr>
<td>Distal perfusion</td>
<td>34 (52.3)</td>
<td>29 (32.2)</td>
<td>0.012</td>
</tr>
<tr>
<td>ECMO-related complication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>3 (4.6)</td>
<td>6 (6.7)</td>
<td>0.735</td>
</tr>
<tr>
<td>Limb ischemia</td>
<td>4 (6.2)</td>
<td>8 (8.9)</td>
<td>0.530</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>1 (1.5)</td>
<td>9 (10.0)</td>
<td>0.046</td>
</tr>
<tr>
<td>ECMO site bleeding</td>
<td>8 (12.3)</td>
<td>10 (11.1)</td>
<td>0.819</td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range) or number (%).
ECPR: extracorporeal cardiopulmonary resuscitation; ECMO: extracorporeal membrane oxygenation; CRRT: continuous renal replacement therapy.

Figure 2. The distribution of patients according to the respiratory quotient. The number of patients according to the respiratory quotient (RQ).

mortality (87.8% vs. 0.0%, P<0.001), shorter length of hospital stay after ECPR (5 vs. 22 days, P<0.001), and higher CPC score (5 vs. 1, P<0.001) compared with patients with good neurologic outcome.

The predictive power of serum lactate level, RQ, and ΔpCO$_2$ for poor neurologic outcome is shown in Figure 3. The AUROC of serum lactate level was 0.635 (95% CI, 0.542–0.727; P<0.001), and the cut-off point was 7.1 (sensitivity and specificity were 60.0 and 66.2, respectively). The AUROC of RQ was 0.609 (95% CI, 0.519–0.699; P<0.001) and the cut-off point was 1.7 (sensitivity and specificity were 72.2 and 49.2, respectively). Finally, the AUROC of ΔpCO$_2$ was 0.579 (95% CI, 0.487–0.670; P<0.001) and the cut-off point was 11.2 (sensitivity and specificity were 43.3 and 75.4, respectively).
Table 3. Initial tissue hypoxia parameters and clinical outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>Good neurologic outcome (n=65)</th>
<th>Poor neurologic outcome (n=90)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial tissue hypoxia parameter</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RQ</td>
<td>1.7 (1.1–2.8)</td>
<td>2.2 (1.5–3.6)</td>
<td>0.021</td>
</tr>
<tr>
<td>ΔpCO₂ (mm Hg)</td>
<td>7.0 (4.6–11.8)</td>
<td>9.7 (5.7–14.8)</td>
<td>0.093</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>5.4 (2.8–10.4)</td>
<td>8.2 (5.1–12.4)</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Clinical outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>0</td>
<td>79 (87.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospital length of stay after ECPR (day)</td>
<td>22.0 (11.5–56.5)</td>
<td>5.0 (2.0–19.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cerebral performance category score</td>
<td>1.0 (1.0–1.0)</td>
<td>5.0 (4.0–5.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range).
RQ: respiratory quotient; ΔpCO₂: venous-arterial difference in CO₂ tension; ECPR: extracorporeal cardiopulmonary resuscitation.

Figure 3. Receiver operating characteristics curves of hypoxia parameters.
RQ: respiratory quotient; ΔpCO₂: venous-arterial difference in CO₂ tension. Values are presented as median (interquartile range).

Predictors for Poor Neurologic Outcome
The results of univariable and multivariable analysis with the logistic regression model for poor neurologic outcome are presented in Table 4. In multivariate analysis, age, CPR to pump-on time, and lactate over 7.1 mmol/L were independently associated with poor neurologic outcome in patients who received ECPR.
DISCUSSION

The current study investigated the ability of RQ measured within the first 24 hours after ECPR to predict neurologic outcomes in a relatively large number of ECPR cases. The main clinical findings of this study were as follows: (1) The median RQ was 2.0 (IQR, 1.4–3.0) after ECPR, which was almost twice the normal value. (2) Although RQ was significantly higher in patients with poor neurologic outcome, it was not independently associated with poor neurologic outcomes in multivariable logistic regression analysis. (3) Among tissue hypoxia markers studied, only serum lactate >7.1 mmol/L was independently associated with poor neurologic outcomes (odds ratio, 2.26; 95% CI, 1.01–5.04; P=0.047).

The clinical significance of RQ has been studied mainly in the context of septic shock. In previous studies involving patients with acute circulatory failure, usually due to septic shock, investigators found that high RQ was associated with absence of improvement in hyperlactemia [10], increase in oxygen consumption after fluid challenge [11,19], and presence of hyperlactemia [16]. In some studies, patients who had both high RQ and hyperlactemia had the worst outcome [20,21]. Finally, higher RQ was also associated indices of microcirculatory failure using near-infrared spectroscopy [22]. These studies suggest that RQ has potential as marker of tissue hypoxia.

In this study, most of the patients had abnormal RQ of >1 which is marked different compared with few small studies performed in post-CPR patients undergoing targetted temperature after ROSC. In this patient population, median RQ values were less than 1.0 [13,23,24]. There are possible explanations for the discrepancy between RQ in patients who received conventional CPR and our ECPR cohort. First, all patients included in studies of RQ after conventional CPR underwent TTM. Hypothermia may diminish the metabolic rate and thus oxygen consumption and carbon dioxide production, which may have influenced RQ values. However, the use of TTM did not affect RQ in this study. RQ was 2.1 (IQR, 1.6–3.4) in patients who received TTM (n=33) and 2.0 (IQR, 1.3–2.9) in patients who did not (n=122) (P=0.493). Second, the timing of blood sampling to calculate RQ was different among studies, which may have influenced the results. Holzinger et al. [13] measured O2 consumption and CO2 production 12 to 24 hours after the patient reached the target temperature of 33 °C. In the study by Uber et al. [23], blood samples were drawn 5.0 to 18.7 hours (median, 9.9 hours) after the ROSC. Third, there may have been selection bias that could have influenced the results. For example, in this study, patients who died within the first 24 hours because of refractory shock were excluded because we wanted to evaluate the clinical significance of tissue hypoxia parameters in patients with the potential to benefit from hemodynamic optimization. Had these patients not been excluded, the level of RQ might have been different. In addition, each study of RQ in conventional CPR patients had different inclusion and exclusion criteria, so the study populations differed slightly.

The prognostic value of serum lactate level in patients after conventional CPR has been reported in previous studies [6,25–27]. Furthermore, lactate is known to be associated with poor clinical outcomes in patients who receive ECMO [28]. Usually, the in vivo production and consumption of lactate balance each other, so that serum lactate levels are constant. However, in local or general tissue hypoxia, impaired mitochondrial oxidation leads to overproduction and underutilization of lactate. Furthermore, combined metabolic acidosis contributes to decreased hepatic removal of lactate [29]. Thus, lactate has been used as a valuable clinical marker to guide resuscitation. It is unclear as to why RQ was inferior to lactate in predicting poor neurologic outcomes in patients who received ECPR in this study. One
Respiratory quotient and poor neurologic outcome

possibility is that blood gas measurements may be influenced by sweep gas and ECMO flow rate, which clinicians could calculate. In their recent study on the theoretical effect of extracorporeal CO₂ removal on native lung RQ, Cipriani et al. suggested that native lung RQ increases when more oxygen is delivered extracorporeally [30]. Although veno-arterial ECMO and extracorporeal CO₂ removal differ in many ways, this may be a clue to explaining the poor utility of RQ as a marker of tissue hypoxia in patients who receive ECPR. In other words, not only tissue hypoxia but also the amount of oxygen delivered by ECMO might have affected RQ in patients who received ECPR. The effect of sweep gas and ECMO flow on RQ needs further investigation.

Second, we used the difference in CO₂ partial pressure as a surrogate for the difference in CO₂ content to calculate RQ. Although there is good correlation between these two values, these two values are not identical, especially when the CO₂ partial pressure is not in the physiological range [11,20,31]. Clinically, calculating serum CO₂ content requires complex equations, making them impractical to be used at the bedside. Therefore, in many stuides, the CO₂ partial pressure is used as a substitute for the CO₂ content in the calculation of the RQ [17,21,22,32]. Third, the exact proportion of ECMO flow compared with native flow in the radial artery could not be measured, which may have influenced blood gas measurements. The proportion of ECMO flow might have increased when native cardiac function decreased. Fourth, the diet might have affected patients’ metabolism and thus the RQ level. Li et al. [33] showed an significant increase in RQ from 0.6 to 1.0 with increasing caloric intake in five pediatric patients receiving ECMO.

There were some limitations to our study. First, this study was conducted with data collected over a long period. During this time, post-arrest management has changed, which could have affected the results. Second, selection bias might have affected the results because this was a retrospective observational study conducted in a single center. In our study, although patients that were excluded due to insufficient data to calculate RQ had similar neurologic outcomes to patients included in this study, some of the outcomes were different between the two groups (data not shown). These differences in different patient groups could have affected the result of this study. Third, to calculate RQ, arterial and venous blood samples drawn within 30 minutes were used in this study. It is not known how this small difference in sampling times could have influenced the overall result. Fourth, more accurate method of measuring RQ such as indirect calorimetry was not used in this study. Future studies using this method may prove to be useful. Finally, although we used a data from a relatively large cohort of ECPR patients, the statistical power might not have been enough. Larger prospective studies are needed to evaluate the utility of RQ as a predictor of poor neurologic outcomes. In patients who received ECPR, RQ was not independently associated with poor neurologic outcome. Further studies on this subject is needed.

CONFLICT OF INTEREST

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

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ORCID

Yun Im Lee https://orcid.org/0000-0001-7939-1275
Ryoung-Eun Ko https://orcid.org/0000-0003-4945-5623
Soo Jin Na https://orcid.org/0000-0002-8551-2472
Jeong-Am Ryu https://orcid.org/0000-0003-1705-848X
Yang Hyun Cho https://orcid.org/0000-0003-1685-3641
Jeong Hoon Yang https://orcid.org/0000-0001-8138-1367
Chi Ryang Chung https://orcid.org/0000-0003-1830-307X
Gee Young Suh https://orcid.org/0000-0001-5473-1712

AUTHOR CONTRIBUTIONS

Conceptualization: YIL, JHY, GYS. Data curation: YIL, REK. Formal analysis: YIL, REK, GYS. Funding acquisition: GYS. Methodology: JHY, CRC, GYS. Project administration: JHY, CRC, GYS. Visualization: YIL, REK. Writing–original draft: YIL, REK, GYS. Writing–review & editing: SJN, JAR, YHC.
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Evaluating diaphragmatic dysfunction and predicting non-invasive ventilation failure in acute exacerbation of chronic obstructive pulmonary disease in India

Nupur B Patel¹, Gaurav Jain¹, Udit Chauhan², Ajeet Singh Bhadoria³, Saurabh Chandrakar¹, Haritha Indulekha¹

¹Department of Anesthesiology and Critical Care, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India
²Department of Radiodiagnosis, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India
³Department of Community and Family Medicine, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India

Background: Baseline diaphragmatic dysfunction (DD) at the initiation of non-invasive ventilation (NIV) correlates positively with subsequent intubation. We investigated the utility of DD detected 2 hours after NIV initiation in estimating NIV failure in acute exacerbation of chronic obstructive pulmonary disease (AECOPD) patients.

Methods: In a prospective-cohort design, we enrolled 60 consecutive patients with AECOPD initiated on NIV at intensive care unit admission, and NIV failure events were noted. The DD was assessed at baseline (T1 timepoint) and 2 hours after initiating NIV (T2 timepoint). We defined DD as ultrasound-assessed change in diaphragmatic thickness (ΔTDI) <20% (predefined criteria [PC]) or its cut-off that predicts NIV failure (calculated criteria [CC]) at both timepoints. A predictive-regression analysis was reported.

Results: In total, 32 patients developed NIV failure, nine within 2 hours of NIV and remaining in next 6 days. The ΔTDI cut-off that predicted NIV failure (DD-CC) at T1 was ≤19.04% (area under the curve [AUC], 0.73; sensitivity, 50%; specificity, 85.71%; accuracy, 66.67%), while that at T2 was ≤35.3% (AUC, 0.75; sensitivity, 95.65%; specificity, 57.14%; accuracy, 74.51%; hazard ratio, 19.55). The NIV failure rate was 35.1% in those with normal diaphragmatic function by PC (T2) versus 5.9% by CC (T2). The odds ratio for NIV failure with DD criteria ≤35.3 and <20 at T2 was 29.33 and 4.61, while that for ≤19.04 and <20 at T1 was 6, respectively.

Conclusions: The DD criterion of ≤35.3 (T2) had a better diagnostic profile compared to baseline and PC in prediction of NIV failure.

Key Words: chronic obstructive pulmonary disease; diaphragmatic dysfunction; diaphragmatic thickness; intubation; non-invasive ventilation

INTRODUCTION

Non-invasive ventilation (NIV) is a first-line therapy in acute exacerbation of chronic obstructive pulmonary disease (AECOPD) intended to support exhausted respiratory muscles to allow early recovery. Patients presenting late usually develop severe acidosis requiring early
intubation [1]. Still, NIV failure remains a dreaded possibility for those tolerating an initial NIV trial [2]. Though studies indicate a positive correlation between baseline diaphragmatic dysfunction (DD) and subsequent NIV failure, such patients may tolerate NIV well if diaphragmatic functions (DFs) recover with NIV support [3,4]. A continued/new-onset DD after NIV initiation may indicate an impending need for intubation.

Various ultrasonographic parameters have been investigated to detect DD in AECOPD [5]. Among these, change in diaphragmatic thickness (ΔTDI) during tidal volume is the most sensitive. Other parameters (diaphragm thickness/velocity/excursion) may incorrectly label diaphragm atrophy in a low-body-weight individual with a thin-healthy diaphragm or miss an acutely paralyzed diaphragm with normal thickness [6]. An ultrasound-assessed ΔTDI value <20% during unassisted spontaneous breathing reflects DD [4,6]. However, the literature is sparse on validated criteria after NIV initiation. We hypothesized that NIV aids in the recovery of DF in some patients with AECOPD; continued or new-onset DD measured at 2 hours after initiating NIV will better identify those with early need for intubation, compared to baseline DD. Our primary objective was to estimate the utility of DD detected 2 hours after initiating NIV in predicting subsequent NIV failure events in AECOPD patients. We defined DD using both predefined (ΔTDI <20%) and calculated criteria (ΔTDI cut-off value). We also estimated the association of baseline DD at admission with NIV failure events.

MATERIALS AND METHODS

Enrolled Population

After All India Institute of Medical Sciences Rishikesh ethical approval (IEC no. AIIMS/IEC/20/111) and obtaining written informed consent, patients aged >18 years of either sex requiring NIV for AECOPD at intensive care unit (ICU) admission between July 2020 and 2021 were included in this prospective, outcome-assessor-blinded, observational cohort trial. We followed all ethical principles for medical research involving human subjects as per the Helsinki Declaration of 2013. The criteria for initiating NIV included acidosis (Paco2 ≥45 mm Hg and arterial pH <7.25) and severe dyspnea, hypoxia, clinical signs of respiratory fatigue, or labored breathing despite supplemental oxygen therapy. We excluded those with acute pulmonary edema, interstitial lung disease, neuromuscular disease, chest-wall deformity, known diaphragmatic palsy, hemodynamic instability, intracranial hypertension, pregnancy, or any contraindication to NIV.

KEY MESSAGES

- Though a positive correlation exists between baseline diaphragmatic dysfunction (DD) and subsequent non-invasive ventilation (NIV) failure, patients experience variable outcomes; thus, a dilemma remains on possible intubation after NIV.
- We observed that the DD criterion of ≤35.3 at 2 hours of NIV had a better diagnostic profile in predicting NIV failure compared to that of <20 in acute exacerbation of chronic obstructive pulmonary disease patients.
- Serial diaphragm evaluation and time-bound DD thresholds may better predict NIV failure and minimize the intricacies of delayed intubation.

Measurement of DD

At ICU admission, we obtained a detailed medical history, performed a clinical examination, and collected baseline lab samples of all enrolled patients per standard institutional protocols. Each patient underwent a baseline diaphragmatic ultrasound in a supine position under B-mode (LOGIC QE, GE Healthcare). A linear ultrasound probe (7–12.0 MHz in a sterile cover) was placed just below the costophrenic sinus and was directed medially, cephalad, and dorsally between an anterior and posterior axillary line to obtain the best orientation of the hemidiaphragm (left/right) at the zone of apposition. We identified the diaphragm in the image as a three-layered structure (depth of 1–3 cm) consisting of a relatively less-echogenic muscle layer between two echogenic lines indicating the peritoneum (deeper) and parietal pleura (superficial). Diaphragmatic thickness (Td) was measured at end-inspiration and expiration under M-mode (T1 timepoint). The measurements were repeated thrice, and the higher Td value was recorded.

All patients were initiated on NIV (Puritan Bennett 840 ventilator, Fisher & Paykel Healthcare) via a non-vented full face mask interface (Best fit-2, Curative Medical Devices) using BIPAP mode, and no sedative was allowed. The NIV settings included an inspiratory positive airway pressure of 10 cm H2O, expiratory positive airway pressure of 5 cm H2O, and 40% fractional inspiratory oxygen, adjusted further to obtain a tidal volume of 8–10 ml/kg, respiratory rate <30 breaths/min, and a target oxygen saturation of 88%–94%. NIV was continued as long as possible on "day 1," for at least sixteen hours on "day 2," and for twelve hours on "day 3." It was discontinued on "day 4" long as possible on "day 1," for at least sixteen hours on "day 2," and for twelve hours on "day 3."
Patel NB, et al. DD to guide intubation after initiating NIV

or later based on clinical judgment or need for invasive ventilation (NIV failure). Indications for initiating invasive ventilation included respiratory/cardiac arrest, hemodynamic instability, no response to IV fluids and vasoactive drugs, arrhythmia, diminished consciousness, psychomotor agitation, aspiration/vomiting, life-threatening hypoxia, or arterial pH <7.25 after 2 hours on NIV. Ultrasonographic measurements were recorded using a similar methodology (on the same side) after 2 hours on NIV (T2 timepoint) or at intubation if a patient failed NIV. All patients received treatment as per standard institutional protocols by a blinded physician and were followed for 30 days post-ICU admission or death, whichever occurred earlier.

The ΔTDI (%) (at both timepoints) was calculated as ((end-inspiration Td–end-expiration Td)/end-expiration Td)×100. The DD was defined using predefined criteria (ΔTDI value <20%) or calculated criteria (ΔTDI cut-off value that predicted subsequent NIV failure at both timepoints). The arterial blood gas (ABG) parameters were measured at T1 and T2 or at the treating physician’s discretion. Other recorded parameters included patient demographics, comorbidities, Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment Score (SOFA) at ICU admission, durations of NIV and invasive ventilation, and ICU/hospital length of stay.

Statistical Analysis
The sample size was calculated using the Open-Epi Collection of Epidemiologic Calculator 3.01 (Andrew G. Dean, Kevin M. Sullivan). We expected an 85% NIV failure rate in patients with AECOPD and DD and a 20% NIV failure rate in those with normal DF after 2 hours on NIV, as estimated from pilot observations (10 patients). Using the "Fleiss with CC" model with a 95% confidence interval (CI) and 80% power, we required 22 patients. To increase the study strength and compensate for those requiring intubation before 2 hours on NIV or any dropouts, we planned to recruit 60 patients. For statistical analysis, we used the IBM SPSS 23.0 (IBM Corp.). The normality of data was assessed by the Kolmogorov-Smirnov test. Results were summarized as mean (standard deviation) or number (%). We analyzed the strength of the association between DD (at T1/T2) and NIV failure by chi-square/Fisher’s exact test, receiver operator characteristic curve, youden index (YI), binary logistic, log-rank, and cox-proportional hazard (PH) regression tests. A P-value<0.05 was considered significant.

RESULTS
Patient Characteristics
In total, 60 patients were included (Figure 1). The majority (67%) had comorbidities at admission, mainly diabetes (35%) and hypertension (28.3%). Baseline ABG parameters showed mixed respiratory acidosis (mean PaCO₂, 64.42) and metabolic alkalosis/acidity (mean pH, 7.20) with varying hypoxia. The baseline mean APACHE II and SOFA scores were 15.7 and 5.18, respectively (Table 1). The mean ΔTDI at T1 was 29.97% (n=60), while that at T2 was 30.05% (n=51); the mean ΔTDI of nine patients intubated before 2 hours was 14%.

Comparison between NIV Success and Failure
In total, 32 patients (53%) developed NIV failure, nine within 2 hours of NIV initiation (mean duration, 55.8 minutes) and the remaining 32 within the next 6 days. The mean time to intubation was 37.21 hours, while the durations of NIV and invasive ventilation were 2.58 and 4.63 days, respectively. Those with

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**Figure 1.** Strengthening the reporting of observational studies in epidemiology (STROBE) flow diagram of patients studied. ICU: intensive care unit; ΔTDI: change in diaphragmatic thickness; NIV: non-invasive ventilation.
NIV failure were primarily males with a smoking history, diabetes, or cor pulmonale but had less frequent hypertension, lower baseline PaCO₂/bicarbonate, lower ∆TDI at T1 and T2, shorter NIV duration, and extended hospital/ICU stay duration (Table 1).

DD Criteria to Predict NIV Failure
The ∆TDI cut-off that predicted subsequent NIV failure (DD calculated criteria) at T1 was ≤19.04% (sensitivity, 50%; specificity, 85.71%; YI, 35.71; accuracy, 66.67%) with an ROC area under the curve (AUC) of 0.73 (95% CI, 0.61–0.86; P=0.002), while that at T2 was ≤35.3% (sensitivity, 95.65%; specificity, 57.14%; YI, 52.80; accuracy, 74.51%) with an AUC of 0.75 (95% CI, 0.62–0.88; P=0.002) (Figure 2, Table 2). Twenty patients (n=60) experienced DD at T1 defined using either calculated (∆TDI ≤19.04%) or predefined criteria (∆TDI <20%), while 34 (continuous, 11; new-onset, 23) versus 14 (continuous, 11; new-onset, 3) had DD at T2 defined by calculated criteria (∆TDI ≤35.3%) or predefined criteria (ΔTDI <20%) (n=51) (Table 3). A significant association was observed between DD and NIV failure at both timepoints, with the highest significance (P=0.002) achieved for the ≤35.3 criterion (Table 3). On univariate analysis, the odds ratio (OR) for NIV failure with DD criterion of ≤35.3 or <20 at T2 was 29.33 and 4.61, respectively, while that for ≤19.04 and <20 at T1 was 6, respectively. The ≤35.3 criterion had better sensitivity (95.65) and accuracy (74.51) but lower specificity (57.14) compared to that of ≤19.04 or <20 (85.71) (Table 2).

Covariates Predicting NIV Failure
On log-rank/Cox-PH analysis of covariates at T1 predicting NIV failure (n=60), male sex (P=0.021), hypertension (P=0.031), heart rate (P=0.011), PaCO₂ (P=0.041), ∆TDI (P=0.002), and number of patients with DD (P=0.001) was associated with NIV failure.

Table 1. Comparison of patients according to NIV outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n=60)</th>
<th>NIV failure (n=32)</th>
<th>NIV success (n=28)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>59±11</td>
<td>58±12</td>
<td>60±11</td>
<td>0.514</td>
</tr>
<tr>
<td>Male</td>
<td>36(60)</td>
<td>24 (67)</td>
<td>12 (33)</td>
<td>0.017</td>
</tr>
<tr>
<td>Smoking history</td>
<td>22 (37)</td>
<td>15 (68)</td>
<td>7 (32)</td>
<td>0.109</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>21 (35)</td>
<td>13 (62)</td>
<td>8 (38)</td>
<td>0.419</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17 (28)</td>
<td>5 (29)</td>
<td>12 (71)</td>
<td>0.024</td>
</tr>
<tr>
<td>Cor pulmonale</td>
<td>12 (20)</td>
<td>8 (67)</td>
<td>4 (33)</td>
<td>0.349</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>12 (20)</td>
<td>6 (50)</td>
<td>6 (50)</td>
<td>1.000</td>
</tr>
<tr>
<td>Steroid use</td>
<td>29 (48)</td>
<td>14 (48)</td>
<td>15 (52)</td>
<td>0.605</td>
</tr>
<tr>
<td>Fever</td>
<td>17 (28)</td>
<td>11 (65)</td>
<td>6 (35)</td>
<td>0.390</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>15.7±2.5</td>
<td>15.6±2.7</td>
<td>15.9±2.2</td>
<td>0.649</td>
</tr>
<tr>
<td>Baseline SOFA score</td>
<td>5.2±2.0</td>
<td>5.0±2.1</td>
<td>5.4±1.8</td>
<td>0.444</td>
</tr>
<tr>
<td>Baseline ABG analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.20±0.08</td>
<td>7.20±0.07</td>
<td>7.20±0.09</td>
<td>0.920</td>
</tr>
<tr>
<td>Lactate</td>
<td>1.8±0.8</td>
<td>1.9±0.8</td>
<td>1.8±0.7</td>
<td>0.632</td>
</tr>
<tr>
<td>PaO₂</td>
<td>81.8±25.9</td>
<td>85.6±27.6</td>
<td>77.5±23.6</td>
<td>0.229</td>
</tr>
<tr>
<td>PaCO₂</td>
<td>64.4±17.4</td>
<td>59.3±12.3</td>
<td>70.3±20.5</td>
<td>0.014</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>25.1±9.3</td>
<td>22.8±5.2</td>
<td>27.8±12.1</td>
<td>0.046</td>
</tr>
<tr>
<td>∆TDI at T1</td>
<td>30.0±15.5</td>
<td>24.4±12.6</td>
<td>37.0±16.0</td>
<td>0.001</td>
</tr>
<tr>
<td>∆TDI at T2/intubation before 2 hours</td>
<td>27.6±14.6</td>
<td>20.6±10.6</td>
<td>35.7±14.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to intubation (hr) (n=32)</td>
<td>37.2±37.6</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Duration of NIV (day)</td>
<td>2.5±1.9</td>
<td>1.6±1.5</td>
<td>3.8±1.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of invasive ventilation (day) (n=32)</td>
<td>4.6±6.2</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ICU stay (day)</td>
<td>8.4±5.0</td>
<td>10.3±6.0</td>
<td>6.3±2.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Hospital stay (day)</td>
<td>10.5±5.5</td>
<td>12.1±6.8</td>
<td>8.6±2.5</td>
<td>0.011</td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation or number (%). NIV: non-invasive ventilation; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; ABG: arterial blood gas; ∆TDI: change in diaphragmatic thickness; T1: at NIV initiation; T2: at 2 hours of NIV; ICU: intensive care unit.
achieved statistical significance, with DD having the highest hazard ratio (HR; 3.15) for NIV failure (T1) (Table 4). Variables of age, smoking history, comorbidities, steroid use, fever, APACHE II score, SOFA score, and other vitals/ABG parameters were not associated with NIV failure. However, multivariate Cox-PH analysis identified baseline heart rate (HR, 1.03; P=0.011) and ΔTDI at admission (HR, 0.96; P=0.004) as significant predictors. Though male sex attained an HR of 2.14, and hypertension had an HR of 0.39, these variables did not attain statistical significance. A similar log-rank/Cox-PH analysis at T2 identified male sex, heart rate (T1), ΔTDI (T2), and DD (T2) as significant predictors among 51 patients who tolerated NIV for the first 2 hours. On multivariable analysis at T2, including either DD by predefined or calculated criterion, parameters including male sex, baseline heart rate, and DD (calculated criteria) achieved statistical significance, with DD having the highest HR (19.55) for NIV failure (calculated criterion) (Table 4). Furthermore, the cumulative hazard for NIV failure was significantly higher for those with DD defined with calculated criteria (≤35.3) compared to predefined criteria (<20) (Figure 3).

DISCUSSION

We observed a 53% NIV failure rate in AECOPD patients initiated on NIV. The DD criterion of ≤35.3 (T2) had a better diagnostic profile and higher log odds and hazard ratio than other thresholds (<20; ≤19.04) in estimating NIV failure. Though the

Table 2. Predictive analysis of NIV failure with respect to DD at both timepoints

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Criteria (ΔTDI)</th>
<th>SE (%)</th>
<th>SP (%)</th>
<th>Accuracy (% 95% CI)</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DD at T1 (PC)</td>
<td>&lt;20.00</td>
<td>50.00</td>
<td>85.71</td>
<td>66.67 (53.31–78.31)</td>
<td>6 (1.69–21.26)</td>
<td>0.006</td>
</tr>
<tr>
<td>DD at T1 (CC)</td>
<td>≤19.04</td>
<td>50.00</td>
<td>85.71</td>
<td>66.67 (53.31–78.31)</td>
<td>6 (1.69–21.26)</td>
<td>0.006</td>
</tr>
<tr>
<td>DD at T2 (PC)</td>
<td>&lt;20.00</td>
<td>43.48</td>
<td>85.71</td>
<td>66.67 (52.08–79.24)</td>
<td>4.61 (1.21–17.65)</td>
<td>0.025</td>
</tr>
<tr>
<td>DD at T2 (CC)</td>
<td>≤35.30</td>
<td>95.65</td>
<td>57.14</td>
<td>74.51 (60.37–85.67)</td>
<td>29.33 (3.45–249.12)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

NIV: non-invasive ventilation; DD: diaphragmatic dysfunction; ΔTDI: change in diaphragmatic thickness; SE: sensitivity; SP: specificity; CI: confidence interval; OR: odds ratio; T1: at NIV initiation; T2: at 2 hours of NIV; PC: predefined criteria; CC: calculated criteria.

Figure 2. Receiver operating characteristic (ROC) curve showing the utility of diaphragmatic dysfunction in predicting non-invasive ventilation (NIV) failure at (A) T1 and (B) T2 timepoints. ΔTDI: change in diaphragmatic thickness; T1: at NIV initiation; T2: at 2 hours into NIV; AUC: area under the curve; CI: confidence interval.
Table 3. Comparison of the association between DD and NIV failure at both timepoints

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NIV failure</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At T1 (PC/CC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DD (n=20)</td>
<td>16 (80.0)</td>
<td>0.006</td>
</tr>
<tr>
<td>No DD (n=40)</td>
<td>16 (40.0)</td>
<td></td>
</tr>
<tr>
<td>At T2 (PC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DD (n=14)</td>
<td>10 (71.4)</td>
<td>0.029</td>
</tr>
<tr>
<td>No DD (n=37)</td>
<td>13 (35.1)</td>
<td></td>
</tr>
<tr>
<td>At T2 (CC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DD (n=34)</td>
<td>22 (64.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No DD (n=17)</td>
<td>1 (5.9)</td>
<td></td>
</tr>
<tr>
<td>DD at T2 (PC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None (n=37)</td>
<td>13 (35.1)</td>
<td>0.066</td>
</tr>
<tr>
<td>New (n=3)</td>
<td>2 (66.7)</td>
<td></td>
</tr>
<tr>
<td>Continuous (n=11)</td>
<td>8 (72.7)</td>
<td></td>
</tr>
<tr>
<td>DD at T2 (CC)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>None (n=17)</td>
<td>1 (5.9)</td>
<td></td>
</tr>
<tr>
<td>New (n=23)</td>
<td>14 (60.9)</td>
<td></td>
</tr>
<tr>
<td>Continuous (n=11)</td>
<td>8 (72.7)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number (%).

DD: diaphragmatic dysfunction; NIV: non-invasive ventilation; T1: at NIV initiation; T2: at 2 hours of NIV; PC: predefined criteria; CC: calculated criteria.

Ultrasound-guided DF assessment is commonly performed at NIV initiation during unassisted spontaneous breathing in AECOPD [3-5, 7]. An ultrasound-depicted ∆TDI value ≤20% at this timepoint indicates DD and risk of NIV failure. We observed a ∆TDI threshold of ≤19.04% for DD at T1, in agreement with the literature. Nine patients failed NIV within 2 hours of initiation; this was an expected outcome considering their lower baseline diaphragmatic reserve (mean ∆TDI, 17) compared to all patients (mean ∆TDI, 29.97). Thus, a baseline ∆TDI threshold ≤20% in this subset of patients successfully predicted impending NIV failure. Among the remaining 51 patients at 2 hours on NIV, one recovered off DD (ΔTDI, 37), eleven had continuous DD (by either criterion), and three developed new-onset DD by predefined criterion and twenty developed new-onset DD by calculated criterion. Among patients with new-onset DD at T2, 14 in the calculated category versus two in the predefined category developed NIV failure. The NIV failure rate was 35.1% (T2) for those defined as having predefined criterion for DD (≤20) had better specificity, the calculated criterion (≤35.3) achieved higher sensitivity and better accuracy in predicting NIV failure.

Table 4. Univariate and multivariable Cox proportional hazards regression analysis for all identified significant predictors of NIV failure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>T1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (male)</td>
<td>2.57</td>
<td>1.15–5.73</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.35</td>
<td>0.13–0.91</td>
</tr>
<tr>
<td>Baseline heart rate (bpm)</td>
<td>1.03</td>
<td>1.0–1.05</td>
</tr>
<tr>
<td>Baseline PaCO₂ (mm Hg)</td>
<td>0.97</td>
<td>0.95–1.0</td>
</tr>
<tr>
<td>ΔTDI at T1</td>
<td>0.96</td>
<td>0.94–0.98</td>
</tr>
<tr>
<td>DD at T1 (PC/CC)</td>
<td>3.15</td>
<td>1.57–6.32</td>
</tr>
<tr>
<td>T2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (male)</td>
<td>2.62</td>
<td>1.03–6.66</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.36</td>
<td>0.12–1.07</td>
</tr>
<tr>
<td>Baseline heart rate (bpm)</td>
<td>1.03</td>
<td>1.0–1.05</td>
</tr>
<tr>
<td>Baseline PaCO₂ (mm Hg)</td>
<td>0.97</td>
<td>0.95–1.0</td>
</tr>
<tr>
<td>ΔTDI at T2</td>
<td>0.96</td>
<td>0.93–0.98</td>
</tr>
<tr>
<td>DD at T2 (CC)</td>
<td>17.0</td>
<td>2.28–126.53</td>
</tr>
<tr>
<td>DD at T2 (PC)</td>
<td>2.52</td>
<td>1.10–5.76</td>
</tr>
</tbody>
</table>

Values are presented as number (%).

DD: diaphragmatic dysfunction; NIV: non-invasive ventilation; HR: hazard ratio; CI: confidence interval; T1: at NIV initiation; T2: at 2 hours of NIV; ΔTDI: change in diaphragmatic thickness; DD: diaphragmatic dysfunction; PC: predefined criteria; CC: calculated criteria.

a) Considering CC; b) Considering PC.
normal DF by a predefined criterion versus 5.9% (T2) for those defined as having normal DF by a calculated criterion. Thus, a cut off of <20% missed a significant proportion of patients who developed NIV failure; a ≤35.3% cut off, in opposition, missed only a single patient. This indicates that a higher ∆TDI threshold better estimates the DD after NIV initiation.

The DD criterion of ≤35.3 at T2 had a higher AUC (0.75) and showed a greater likelihood of NIV failure (OR, 29.33) than a threshold of ≤19.04 (AUC, 0.73; OR, 6). Cammarota et al. [7] also observed a higher AUC (0.98) for diaphragmatic excursion at one hour after initiating NIV compared to baseline values. Marchioni et al. [3] showed that AECOPD patients with DD at NIV initiation had a higher risk of NIV failure (HR, 6.2) compared to those with normal DF. While we could not identify studies evaluating ∆TDI after initiating NIV, similar thresholds were observed for ∆TDI as a predictor of successful weaning in ICU patients [8,9]. The univariate-Cox model estimated an HR of 17 by the DD criterion of ≤35.3, while an HR of 3.15 was estimated using other criteria (<20; ≤19.04) to predict NIV failure. The multivariate Cox-PH analysis indicated an even higher HR of 19.55 for the criterion of ≤35.3, while other criteria (<20; ≤19.04) did not attain statistical significance. The cumulative hazard of NIV failure was significant using a calculated criterion for DD (≤35.3).

The etiology of DD during AECOPD is multifactorial, involving both acute and chronic pathophysiological elements [10-12]. Though underlying chronic inflammation and steroid-induced diaphragmatic damage play a vital role, studies could not identify a comparable difference in ultrasound-assessed DF between those with stable COPD and healthy individuals [13]. This indicates some degree of diaphragmatic reserve in stable COPD that could not endure the increased workload and mechanical stress of AECOPD, leading to amplified functional diaphragmatic exhaustion/dysfunction during acute exacerbation. NIV is the first-line treatment intended to assist respiratory muscles, improve gaseous exchange, and thereby reduce the intubation rate in such patients [14,15]. Patients who respond to NIV have an improved pH within 1–4 hours after NIV initiation; hence, it is advisable to look for NIV failure as early as 2 hours after initiation [2,16,17]. We performed ∆TDI measurements 2 hours into NIV with this consideration. Moreover, some AECOPD patients with normal DF at ICU admission may develop NIV failure, while others with DD do not require intubation. This indicates the recovery/deterioration of DF after initiating NIV. Corbellini et al. [18] also reported an improvement in diaphragmatic mobility after in-patient pulmonary rehabilitation in AECOPD patients. Thus, repeat DF assessment after NIV initiation seems logical to identify those in need of intubation.

The significant Cox-covariates predicting NIV failure were male sex, hypertension, higher baseline heart rate, and hypercarbia. Studies have variably associated parameters of pH, hypercarbia, respiratory/heart rate, APACHE II score, and comorbidities with NIV failure [10,16]. An underlying difference in statistical interpretation (logistic vs. Cox regression) and sample size could contribute to such differences. Further-
more, inherent differences in unaccounted factors, including ethnicity, demographics, lifestyle, late hospital presentation, comorbidities, and organ reserve, could also account for such secondary outcomes. Still, a DD criterion of ≤35.3 showed adequate prediction of NIV failure.

Our study has some strengths. First, all studied timepoints were practically achievable and precisely analyzed in all included patients. Second, a skilled investigator with 5 years of ultrasound experience performed the sonographic measurements, and the outcome assessors were blinded to all other aspects; this allowed homogeneity in measurements and added to the authenticity of results. Our study has a few limitations. We performed ΔTDI estimation at two timepoints only. A serial time-bound analysis during the first 24 hours of NIV may better delineate DF changes and be an ideal review point for estimating NIV failure. Second, due to logistic issues, we could not evaluate the effect of lung hyperinflation during AECOPD. The relationship between lung volume change and ΔTDI after NIV initiation could better delineate the pathophysiological recovery and should be tested in future trials. Third, AECOPD could have a broad range of precipitating causes. An underlying difference in acute pulmonary pathophysiological/radiological involvement in different precipitants may also affect the underlying diaphragmatic reserve and possibly ΔTDI thresholds. To negate the effect of regional differences, we performed ΔTDI estimation on both hemidiaphragms and considered the best value for analysis.

In conclusion, a DD criterion of ≤35.3 at 2 hours after initiating NIV in AECOPD patients had a better diagnostic profile in predicting NIV failure compared to baseline or predefined criteria. Serial diaphragm evaluation and time-bound DD thresholds may better predict NIV failure, compared to single timepoint measurements and minimize intricacies related to delayed intubation.

CONFLICT OF INTEREST

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

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ORCID

Nupur B Patel https://orcid.org/0000-0001-9929-0391
Gaurav Jain https://orcid.org/0000-0002-1205-7237
Udit Chauhan https://orcid.org/0000-0003-0078-8240
Ajeet Singh Bhadoria https://orcid.org/0000-0002-6947-7910
Saurabh Chandrakar https://orcid.org/0000-0003-2449-2153
Haritha Indulekha https://orcid.org/0000-0001-7475-1809

AUTHOR CONTRIBUTIONS

Conceptualization: NBP, GJ. Data curation: NBP, UC, SC, HI. Formal analysis: GJ, ASB. Methodology: GJ, ASB. Project administration: GJ. Visualization: GJ. Writing—original draft: NBP, GJ. Writing—review & editing: GJ, UC, ASB, SC, HI.

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Subjects with acute hypercapnic respiratory failure admitted to the emergency department. Respir Care 2019;64:1469-77.


Percent fluid overload for prediction of fluid de-escalation in critically ill patients in Saudi Arabia: a prospective observational study

Reham A. Alharbi¹, Namareq F. Aldardeer¹, Emily L. G. Heaphy², Ahmad H. Alabbasi³, Amjad M. Albuqami⁴, Hassan Hawa⁵

¹Department of Pharmaceutical Care, King Faisal Specialist Hospital and Research Center, Jeddah, Saudi Arabia
²Department of Research, King Faisal Specialist Hospital and Research Center, Jeddah, Saudi Arabia
³Nahdi Medical Company, Medina, Saudi Arabia
⁴United Pharmacy, Jeddah, Saudi Arabia
⁵Department of Critical Care Medicine, King Faisal Specialist Hospital and Research Center, Jeddah, Saudi Arabia

Background: Percent fluid overload greater than 5% is associated with increased mortality. The appropriate time for fluid deresuscitation depends on the patient's radiological and clinical findings. This study aimed to assess the applicability of percent fluid overload calculations for evaluating the need for fluid deresuscitation in critically ill patients.

Methods: This was a single-center, prospective, observational study of critically ill adult patients requiring intravenous fluid administration. The study's primary outcome was median percent fluid accumulation on the day of fluid deresuscitation or intensive care unit (ICU) discharge, whichever came first.

Results: A total of 388 patients was screened between August 1, 2021, and April 30, 2022. Of these, 100 with a mean age of 59.8±16.2 years were included for analysis. The mean Acute Physiology and Chronic Health Evaluation (APACHE) II score was 15.4±8.0. Sixty-one patients (61.0%) required fluid deresuscitation during their ICU stay, while 39 (39.0%) did not. Median percent fluid accumulation on the day of deresuscitation or ICU discharge was 4.5% (interquartile range [IQR], 1.7%–9.1%) and 5.2% (IQR, 2.9%–7.7%) in patients requiring deresuscitation and those who did not, respectively. Hospital mortality occurred in 25 (40.9%) of patients with deresuscitation and six (15.3%) patients who did not require it (P=0.007).

Conclusions: The percent fluid accumulation on the day of fluid deresuscitation or ICU discharge was not statistically different between patients who required fluid deresuscitation and those who did not. A larger sample size is needed to confirm these findings.

Key Words: critical care; de-escalation; fluid overload; prospective

INTRODUCTION

Intravenous (IV) fluid is a common intervention in intensive care units (ICUs) [1,2]. IV fluid is often administered in large volumes in critically ill patients to improve cardiac output and ameliorate shock [3,4]. Upon hemodynamic stability, patients often receive variable amounts...
of fluid therapy [5]. However, IV fluid can carry significant risks to critically ill patients [6]. Fluid overload (FO) is a common complication in critically ill patients, with an incidence ranging from 30% to 70% [7-9]. FO is defined as cumulative fluid balance (FB) greater than 10% of body weight [10,11]. Positive cumulative FB has been reported in up to 40% of patients admitted to the ICU [12]; Moreover, several studies have shown that a persistent cumulative positive FB negatively impacts ICU patient outcomes [2,13]. In patients with acute lung injury, positive FB was associated with further impaired oxygenation and prolonged need for mechanical ventilation [11,14]. On the other hand, negative FB has been advocated for as an indication of early cessation of mechanical ventilation [6]. Some observational studies have reported negative FB to be associated with lower risk-adjusted short-term mortality compared to patients with positive FB [12].

The term deresuscitation or de-escalation was first suggested in 2012, and finally coined in the literature in 2014 [13]. Deresuscitation or de-escalation refers to the phase of critical illness after initial resuscitation, stabilization, and optimization [15]. Deresuscitation is widely practiced mitigating the potential harm of FO. The active deresuscitation phase is initiated when FO is clinically identified and hemodynamic stability has been attained and should be assessed daily [16].

Information about the appropriate timing of fluid deresuscitation mainly depends on physician assessment of patient clinical and radiological findings. Historically, many studies have found a relationship between calculated percent FO greater than 5% and mortality [10,12,17]. However, none of the studies evaluated the relationship between percent FO and need for fluid deresuscitation. Therefore, our study aimed to assess the applicability of percent FO calculation for evaluating the need for fluid deresuscitation by diuretics and/or renal replacement therapy (RRT) in critically ill patients.

**MATERIALS AND METHODS**

**Ethics Approval and Consent to Participate**

A single-center, prospective, observational study was conducted between August 01, 2021, and April 30, 2022. The study was approved by the King Faisal Specialist Hospital and Research Center Institutional Review Board, Jeddah, Saudi Arabia (No. 2021-19). To ensure patient privacy and confidentiality, limited data access was available to study investigators. Informed consent from study participants was waived by the board due to the study’s observational nature. The study was conducted in accordance with local regulations, and ethical principles were ensured in accordance with the Declaration of Helsinki.

**Patients**

Enrollment criteria include patients 18 years old or older who were admitted to the medical ICU and received IV fluids, including colloids and/or crystalloids, as a replacement or resuscitation. Exclusion criteria were age <18 years, end-stage renal disease, on hemodialysis, on diuretics upon ICU admission, on maintenance IV fluids >72 hours before ICU admission, started on RRT 24 hours post-ICU admission, on the diabetic ketoacidosis or hyperosmolar hyperglycemic state protocol, or inability to measure fluid output (Supplementary Figure 1).

**Data Collection**

Data screening occurred each Sunday, excluding holidays. All patients who fulfilled the criteria were considered for inclusion. Patients were followed until the day of deresuscitation by diuretics, RRT, or ICU discharge, whichever came first. The total amount of fluid administered including IV resuscitation fluids, IV maintenance fluid, IV medications, and total parenteral nutrition was calculated every 24 hours until deresuscitation or ICU discharge. We also collected information on comorbidities, severity scores, acute kidney injury, use of mechanical ventilation (MV), and FB. Patient data were collected and handled using Research Electronic Data Capture (REDCap) software.

**Outcomes**

This study’s primary outcome of interest is the median percent fluid accumulation on the day of fluid deresuscitation or ICU discharge, whichever comes first. Secondary outcomes were median FB at 24, 48, and 72 hours of ICU stay; duration of
mechanical ventilation; length of hospital and ICU stays; and ICU and hospital mortality. Primary exposures of interest were Acute Physiology and Chronic Health Evaluation (APACHE) II score, diagnosis of acute respiratory distress syndrome (ARDS) upon ICU admission and need for mechanical ventilation. Other characteristics of interest were age, gender, weight, body mass index, source of ICU admission, other ICU admission diagnoses, comorbidities, need for vasopressors, use of nephrotoxic drugs, and whether a Foley catheter was removed before ICU discharge or starting diuretics or RRT.

Definitions
Percent FO was defined as the total cumulative FB in liters from ICU admission to the first of fluid deresuscitation or ICU discharge divided by patient baseline weight upon hospital admission, multiplied by 100 [11]. Our study calculated percent FO only for patients with positive FB at deresuscitation. Fluid deresuscitation or de-escalation is defined as active fluid removal through diuretics and RRT with net ultrafiltration [15].

Sample Size and Statistical Analysis
No previous studies have investigated percent FO as a primary outcome. For this reason, an adequate sample size could not be estimated. All patients who fulfilled the inclusion criteria during the study period were enrolled. The normality of the continuous predictor variables was assessed using Shapiro-Wilk and Kolmogorov-Smirnov tests by comparing median and mean values and observing the data graphically. The associations between exposure variables, baseline and clinical characteristics, and fluid deresuscitation status were assessed using Student t-test, Wilcoxon two-sample test with normal approximation, chi-square test, and Fisher’s Exact Test. The associations between predictor variables and hospital mortality also were assessed using these bivariate tests, as were the associations between patient fluid and mortality outcomes by fluid deresuscitation status. Fluid outcomes were also evaluated at 24-, 48-, and 72-hour post-ICU discharge. A multivariable logistic model adjusted for age, APACHE II score, deresuscitation status, ARDS, and need for MV at baseline was constructed to examine the associations between the primary exposures of interest and hospital mortality. Analyses were performed using SAS analytics software ver. 9.4 (SAS Institute), and statistical significance was determined at an α=0.05 level.

RESULTS
The study population included 100 ICU patients with a mean age of 59.8 years and a male proportion of 57.0%. A total of 57.0% of the patients required mechanical ventilation (Table 1), and 61.0% of the patients underwent fluid deresuscitation with either diuretic, RRT, or both. Specifically, 59% of patients received diuretics, while 18.0% underwent RRT (Supplementary Table 1). The median time from ICU admission to diuretic therapy was 2.0 days (interquartile range [IQR], 1.0–4.0), and the median time from ICU admission to RRT was 4.0 days (IQR, 2.0–9.0) (Supplementary Table 1).

The patients who received fluid deresuscitation were significantly older, with a mean age of 62.5 years, compared to patients who did not receive fluid deresuscitation, with a mean age of 55.6 years (P=0.036) (Table 1). The mean APACHE II

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n=100)</th>
<th>Fluid de-resuscitation (n=61)</th>
<th>No fluid de-resuscitation (n=39)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>59.8±16.2</td>
<td>62.5±16.7</td>
<td>55.6±14.6</td>
<td>0.036</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td>0.356</td>
</tr>
<tr>
<td>Male</td>
<td>57 (57.0)</td>
<td>37 (64.9)</td>
<td>20 (35.1)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>43 (43.0)</td>
<td>24 (55.8)</td>
<td>19 (44.2)</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>72.9±18.3</td>
<td>73.5±17.6</td>
<td>72.0±19.7</td>
<td>0.682</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.5±6.3</td>
<td>27.3±5.9</td>
<td>27.7±7.0</td>
<td>0.794</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>15.4±8.0</td>
<td>17.2±7.1</td>
<td>12.4±8.6</td>
<td>0.003</td>
</tr>
<tr>
<td>Source of ICU admission</td>
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<td></td>
<td></td>
<td>0.009</td>
</tr>
<tr>
<td>Emergency department</td>
<td>20 (20.0)</td>
<td>16 (80.0)</td>
<td>4 (20.0)</td>
<td></td>
</tr>
<tr>
<td>Hospital floor</td>
<td>42 (42.0)</td>
<td>27 (64.3)</td>
<td>15 (35.7)</td>
<td></td>
</tr>
<tr>
<td>Operating room</td>
<td>26 (26.0)</td>
<td>9 (34.6)</td>
<td>17 (65.4)</td>
<td></td>
</tr>
<tr>
<td>Another hospital</td>
<td>12 (12.0)</td>
<td>9 (75.0)</td>
<td>3 (25.0)</td>
<td></td>
</tr>
</tbody>
</table>

(Continued to the next page)
Table 1. Continued

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n=100)</th>
<th>Fluid deresuscitation (n=61)</th>
<th>No fluid deresuscitation (n=39)</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td><strong>ICU admission diagnosis</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septic shock</td>
<td>18 (18.0)</td>
<td>10 (55.6)</td>
<td>8 (44.4)</td>
<td>0.601</td>
</tr>
<tr>
<td>Hemorrhagic shock</td>
<td>9 (9.0)</td>
<td>6 (66.7)</td>
<td>3 (33.3)</td>
<td>1.000</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>8 (8.0)</td>
<td>7 (87.5)</td>
<td>1 (12.5)</td>
<td>0.145</td>
</tr>
<tr>
<td>ARDS</td>
<td>13 (13.0)</td>
<td>12 (92.3)</td>
<td>1 (7.7)</td>
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<tr>
<td>Neurological illness (status epilepticus, stroke)</td>
<td>25 (25.0)</td>
<td>18 (72.0)</td>
<td>7 (28.0)</td>
<td>0.193</td>
</tr>
<tr>
<td>Other</td>
<td>42 (42.0)</td>
<td>17 (40.5)</td>
<td>25 (59.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Comorbidity</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic/valvular heart disease</td>
<td>21 (21.0)</td>
<td>15 (71.4)</td>
<td>6 (28.6)</td>
<td>0.270</td>
</tr>
<tr>
<td>Systolic HF</td>
<td>2 (2.0)</td>
<td>2 (100.0)</td>
<td>0</td>
<td>0.519</td>
</tr>
<tr>
<td>Diastolic HF</td>
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<td>2 (100.0)</td>
<td>0</td>
<td>0.519</td>
</tr>
<tr>
<td>Diabetes</td>
<td>41 (41.0)</td>
<td>30 (73.2)</td>
<td>11 (26.8)</td>
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<tr>
<td>Hypertension</td>
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<td>Liver cirrhosis</td>
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<td>1 (1.0)</td>
<td>0</td>
<td>1.000</td>
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<tr>
<td>Liver disease (HCV, HBV, ALF)</td>
<td>4 (4.0)</td>
<td>4 (4.0)</td>
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<td>0.154</td>
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<tr>
<td>Chronic respiratory disorder</td>
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<td>5 (62.5)</td>
<td>3 (37.5)</td>
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</tr>
<tr>
<td>Hematologic malignancy</td>
<td>8 (8.0)</td>
<td>7 (87.5)</td>
<td>1 (12.5)</td>
<td>0.145</td>
</tr>
<tr>
<td>Non-hematologic malignancy</td>
<td>16 (16.0)</td>
<td>7 (43.8)</td>
<td>9 (56.2)</td>
<td>0.123</td>
</tr>
<tr>
<td>HIV infection</td>
<td>1 (1.0)</td>
<td>0</td>
<td>1 (100.0)</td>
<td>0.390</td>
</tr>
<tr>
<td>BMT</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>SOT</td>
<td>2 (2.0)</td>
<td>1 (50.0)</td>
<td>1 (50.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>9 (9.0)</td>
<td>6 (66.7)</td>
<td>3 (33.3)</td>
<td>1.000</td>
</tr>
<tr>
<td>Epilepsy disorder</td>
<td>5 (5.0)</td>
<td>2 (40.0)</td>
<td>3 (60.0)</td>
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</tr>
<tr>
<td>Other</td>
<td>-</td>
<td>31 (55.4)</td>
<td>25 (44.6)</td>
<td>0.192</td>
</tr>
<tr>
<td>None</td>
<td>-</td>
<td>3 (27.3)</td>
<td>8 (72.7)</td>
<td>0.022</td>
</tr>
<tr>
<td>Required vasopressor</td>
<td>68 (68.0)</td>
<td>45 (66.2)</td>
<td>23 (33.8)</td>
<td>0.122</td>
</tr>
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<td>Required mechanical ventilation</td>
<td>57 (57.0)</td>
<td>42 (73.7)</td>
<td>15 (26.3)</td>
<td>0.003</td>
</tr>
<tr>
<td>Patient who had ARF upon ICU admission</td>
<td>30 (30.0)</td>
<td>24 (80.0)</td>
<td>6 (20.0)</td>
<td>0.011</td>
</tr>
<tr>
<td><strong>Use of nephrotoxic drugs prior to use of diuretics or RRT</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminoglycoside</td>
<td>7 (7.0)</td>
<td>7 (100.0)</td>
<td>0</td>
<td>0.041</td>
</tr>
<tr>
<td>Colistin</td>
<td>3 (3.0)</td>
<td>3 (100.0)</td>
<td>0</td>
<td>0.279</td>
</tr>
<tr>
<td>NSAID</td>
<td>15 (15.0)</td>
<td>11 (73.3)</td>
<td>4 (26.7)</td>
<td>0.288</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>4 (4.0)</td>
<td>4 (100.0)</td>
<td>0</td>
<td>0.154</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>35 (35.0)</td>
<td>24 (68.6)</td>
<td>11 (31.4)</td>
<td>0.255</td>
</tr>
<tr>
<td>Other</td>
<td>50 (50.0)</td>
<td>30 (60.0)</td>
<td>20 (40.0)</td>
<td>0.838</td>
</tr>
<tr>
<td>Foley catheter removed before ICU discharge or starting diuretics/RRT</td>
<td>17 (17.0)</td>
<td>6 (35.3)</td>
<td>11 (64.7)</td>
<td>0.017</td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation or number (%).
BMI: body mass index; APACHE: Acute Physiology and Chronic Health Evaluation; ICU: intensive care unit; ARDS: acute respiratory distress syndrome; HF: heart failure; HCV: hepatitis C virus; HBV: hepatitis B virus; ALF: acute liver failure; HIV: human immunodeficiency virus; BMT: bone marrow transplantation; NA: not applicable; SOT: solid organ transplant; ARF: acute renal failure; RRT: renal replacement therapy; NSAID: non-steroidal anti-inflammatory drug.

a) Fluid deresuscitation defined as need for diuretics and/or renal replacement therapy; b) Percentages may total >100 due to multiple diagnoses, conditions, and/or prescriptions.
score was also significantly higher for patients that received fluid deresuscitation compared to those who did not (17.2 vs. 12.4, P=0.003). The association between ICU admission diagnosis of ARDS and need for fluid deresuscitation was significant, with 92.3% of the patients diagnosed with ARDS requiring fluid deresuscitation compared to 7.7% of ARDS patients not needing fluid de-resuscitation (P=0.014) (Table 1).

Median percent fluid accumulation on the day of deresuscitation or ICU discharge was 4.5% (IQR, 1.7%–9.1%) and 5.2% (IQR, 2.9%–7.7%) in patients who required deresuscitation and those who did not, respectively (P=0.723). The median total fluid intake on the day of ICU discharge was significantly higher among patients that did not receive fluid deresuscitation (7,029.5 ml; IQR, 4,904.6–9,354.0 ml) compared to patients that did (5,274.8 ml; IQR, 2,580.5–8,862.8 ml) (P=0.049) (Table 2). Indeed, fluid intake and total fluid cumulative balance varied based on the time of deresuscetation (Supplementary Table 2). ICU length of stay was 16.3 (IQR, 8.0–24.1) vs. 2.35 (IQR, 0.8–7.4) days (P<0.001), and hospital length of stay was 25.4 (IQR, 15.5–54.9) vs. 8.4 (IQR, 5.8–17.6) days (P=0.001) (Table 2). A total of 31 patients (31.0%) experienced hospital mortality in our cohort (Supplementary Table 3).

In the multivariable model controlling for the main exposure variables, higher APACHE II score was associated with increased likelihood of hospital mortality, and patients were 20% more likely to die in the hospital with every one-unit increase in score (adjusted odds ratio, 1.2; 95% confidence interval [CI], 1.1–1.3; P<0.001) (Table 3).

### DISCUSSION

This single-center, observational study was conducted to assess the applicability of percent FO calculation for evaluating the need for fluid deresuscitation in critically ill patients. Many studies have used percent FO calculation as a cutoff to define FO or fluid accumulation [10,11,17].

Our study found no statistically significant differences in median percent fluid accumulation on the day of deresuscitation or ICU discharge in patients who did not require fluid deresuscitation, with a value of 5.2% (2.9%–7.7%) compared to the 4.5% (1.7%–9.1%) in patients who received deresuscitation of fluid (P=0.723). However, the median total volume of fluid administered was significantly higher in patients in the no deresuscitation arm (7,029.5 ml; IQR, 4,904.6–9,354.0 ml) than in the deresuscitation arm (5,274.8 ml; IQR, 2,580.5–8,862.8 ml) (P=0.049). These findings can explain the lack of relationship among amount of fluid administered, percent fluid accumulation, and need for fluid deresuscitation.

### Table 2. Patient outcomes by fluid deresuscitation status (n=100)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Total</th>
<th>Fluid deresuscitation</th>
<th>No fluid deresuscitation</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid accumulation on the day of ICU discharge/outcome (%)</td>
<td>4.7 (2.4–8.6)</td>
<td>4.5 (1.7–9.1)</td>
<td>5.2 (2.9–7.7)</td>
<td>0.723</td>
</tr>
<tr>
<td>The total fluid intake on the day of ICU discharge/outcome (ml)</td>
<td>5,738.7 (3,892.5–9,294.3)</td>
<td>5,274.8 (2,570.5–8,862.8)</td>
<td>7,029.5 (4,904.6–9,354.0)</td>
<td>0.049</td>
</tr>
<tr>
<td>Total fluid output on the day of ICU discharge/outcome (ml)</td>
<td>2,637.5 (1,362.5–6,111.0)</td>
<td>2,480.0 (1,185.0–6,555.0)</td>
<td>2,730.0 (1,710.0–5,520.0)</td>
<td>0.478</td>
</tr>
<tr>
<td>Total fluid balance on the day of ICU discharge/outcome (ml)</td>
<td>2,296.3 (53.0–4,512.7)</td>
<td>1,762.8 (–157.7 to 4572.6)</td>
<td>2,730.3 (1,163.0–4,452.8)</td>
<td>0.355</td>
</tr>
<tr>
<td>Total cumulative fluid balance at 24 hours (ml)</td>
<td>1,609.8 (440.5–3,219.6)</td>
<td>1,174.0 (–56.5 to 3,067.8)</td>
<td>2,258.0 (1,009.0–3,779.1)</td>
<td>0.091</td>
</tr>
<tr>
<td>Total cumulative fluid balance at 48 hours (n=62, ml)</td>
<td>2,132.0 (918.5–3,100.0)</td>
<td>1,019.4 (–130.0 to 2,148.8)</td>
<td>2,258.0 (1,009.0–3,779.1)</td>
<td>0.816</td>
</tr>
<tr>
<td>Total cumulative fluid balance at 72 hours (n=34, ml)</td>
<td>295.3±1,170.4</td>
<td>217.9±1,191.3</td>
<td>393.4±1,177.2</td>
<td>0.671</td>
</tr>
<tr>
<td>Duration of MV (day)</td>
<td>8.0 (4.0–14.0)</td>
<td>9.0 (5.0–15.0)</td>
<td>4.0 (1.0–8.0)</td>
<td>0.004</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>26 (26.0)</td>
<td>21 (34.4)</td>
<td>5 (12.8)</td>
<td>0.016</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>31 (31.0)</td>
<td>25 (40.9)</td>
<td>6 (15.3)</td>
<td>0.007</td>
</tr>
<tr>
<td>Length of ICU stay (day)</td>
<td>9.0 (2.9–18.5)</td>
<td>16.3 (8.0–24.1)</td>
<td>2.35 (0.8–7.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Length of hospital stay (day)</td>
<td>17.6 (8.3–42.6)</td>
<td>25.4 (15.5–54.9)</td>
<td>8.4 (5.8–17.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range), mean±standard deviation, or number (%). ICU: intensive care unit; MV: mechanical ventilation.

a) Fluid deresuscitation or de-escalation is defined as the need for diuretics and/or renal replacement therapy; b) Represent patients with positive fluid balance on the ICU discharge/outcome day. A total of 44 patients were in the fluid deresuscitation group vs. 31 in the no fluid deresuscitation group.
Several studies have demonstrated an association of percent FO with mortality [10,11,17]. Our study showed that mortality was significantly higher in patients who required fluid deresuscitation than in those who did not (ICU mortality: 34.4% vs. 12.8%; P=0.016) and hospital mortality (40.9% vs. 15.3%; P=0.007). This is explained by the higher mean APACHE II score in the patients who required fluid deresuscitation during their ICU stay, representing the sicker group (17.2±7.1 and 12.4±8.6; P=0.003). In the multivariable logistic model, APACHE II score was a significant predictor of hospital mortality (OR, 1.2; 95% CI, 1.1–1.3). On the other hand, a recent study found a significant reduction in ICU length of stay (mean difference, -1.88 days; 95% CI, -0.12 to -3.64) with de-resuscitative strategies compared to the standard approach [3]. In our observational study, lengths of stay in the ICU and in the hospital overall were significantly longer for sicker patients requiring fluid deresuscitation.

In our study, 18% of the patients presented with septic shock. Approximately 55% of patients required fluid deresuscitation during their ICU stay. Positive FB in patients with sepsis was associated with poor 28-day survival and with increased 60-day survival of patients with acute renal failure [7]. A retrospective study that investigated fluid administration in early sepsis and septic shock found that administration of more than 5 L of fluid on the first day of shock was associated with increased mortality [18]. Subsequent studies have proposed that "fluid accumulation" or "positive fluid balance" in septic patients is mainly related to the severity of illness and is a marker of poor outcome [19,20]. However, the recent Restriction of Intravenous Fluid in ICU Patients with Septic Shock (CLASSIC) study randomized 1,554 patients with septic shock to a fluid restrictive or standard care protocol. The study did not find a mortality benefit of a fluid restriction strategy in sepsis [21].

The duration of mechanical ventilation is a crucial outcome of interest in fluid studies. In a systematic review and meta-analysis of the restrictive fluid approach in adult patients with septic shock, a longer duration of ventilator-free days was observed with the de-resuscitate strategy [22]. However, in the Role of Active Deresuscitation After Resuscitation-2 (RADA-2) study, no significant difference in ventilator-free days was found among critically ill patients who underwent active fluid deresuscitation compared with usual care [3]. In our observational study, mechanical ventilation days were higher in number in the sicker group who required fluid deresuscitation by either diuretics or RRT (median, 9 days; IQR, 5.0–15.0 vs. 4 days, 1.0–8.0; P=0.004).

The patients included in our analysis broadly represent those treated in the ICU and reflect real-world practice. Our study was the first to describe the average range of percent FO that required deresuscitation in critically ill patients. However, it had several limitations, including the observational nature, the small sample size, and the lack of study power. In addition, the difference in baseline APACHE II scores between the two comparative arms might have affected the outcome. The study did not investigate the number of blood transfusions administered to patients, the amount of fluid removed during the dialysis sessions, or the clinician reported reason for fluid deresuscitation. Future studies are warranted to guide the appropriate timing for fluid de-resuscitation among critically ill patients using specific clinical and radiological criteria. Moreover, larger studies testing the possibility of percent overload calculations as a guide for the need for fluid de-resuscitation or a tool for patient fluid assessment are needed.

In conclusion, our observational study found that percent fluid accumulation calculation on the day of deresuscitation or ICU discharge was not significantly different between patients requiring fluid deresuscitation and those who did not. Thus, percent FO cannot be considered as a predictive tool for fluid deresuscitation. A study with a larger sample size is needed to confirm these findings.

### Table 3. Multivariable logistic model for the factors affecting hospital mortality (n=100)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariable</th>
<th>P-value</th>
<th>Multivariable</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>1.0 (1.0–1.1)</td>
<td>0.018</td>
<td>1.0 (1.0–1.0)</td>
<td>0.918</td>
</tr>
<tr>
<td>Fluid deresuscitation</td>
<td>3.8 (1.4–10.5)</td>
<td>0.009</td>
<td>2.1 (0.6–7.7)</td>
<td>0.255</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>1.2 (1.1–1.3)</td>
<td>&lt;0.001</td>
<td>1.2 (1.1–1.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ARDS diagnosis upon ICU admission</td>
<td>6.6 (1.9–23.7)</td>
<td>0.004</td>
<td>2.6 (0.6–12.5)</td>
<td>0.226</td>
</tr>
<tr>
<td>Need for mechanical ventilation</td>
<td>4.8 (1.8–13.2)</td>
<td>0.002</td>
<td>2.4 (0.7–7.9)</td>
<td>0.166</td>
</tr>
</tbody>
</table>

OR: odds ratio; CI: confidence interval; APACHE: Acute Physiology and Chronic Health Evaluation; ARDS: acute respiratory distress syndrome; ICU: intensive care unit.
CONFLICT OF INTEREST

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

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ORCID

Reham A. Alharbi https://orcid.org/0000-0001-6773-5624
Namareq F. Aldardeer https://orcid.org/0000-0001-9323-1606
Ahmad H. Alabbasi https://orcid.org/0000-0003-0811-8820
Amjad M. Albuqami https://orcid.org/0000-0003-2543-801X
Hassan Hawa https://orcid.org/0000-0001-6773-5624

AUTHOR CONTRIBUTIONS

Conceptualization: HH, NFA. Methodology: HH, NFA. Formal analysis: ELGH. Data curation: RAA, AHA, AMA, NFA. Visualization: NFA. Project administration: NFA. Writing—original draft: RAA, NFA. Writing—review & editing: NFA.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4266/acc.2022.01550.

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Epidemiology and outcome of an acute kidney injuries in the polytrauma victims admitted at the apex trauma center in Dubai

Bhushan Sudhakar Wankhade1,2, Zeyad Faoor Alrais1,2, Ghaya Zeyad Alrais3, Ammar Mohamed Abdel Hadi1, Gopala Arun Kumar Naidu1, Mohammed Shahid Abbas1, Ahmed Tarek Youssef Aboul Kheir1, Hasan Hadad4, Sundareswaran Sharma2, Mohammad Sait2

1Department of Surgical Intensive Care Medicine, Rashid Hospital, Dubai, UAE
2College of Medicine, Mohammed Bin Rashid University of Medicine and Health Sciences, Dubai, UAE
3Dubai Medical College, Dubai, UAE
4Emergency Department, Emirates Hospital, Jumeirah, Dubai, UAE

Background: Polytrauma from road accidents is a common cause of hospital admissions and deaths, frequently leading to acute kidney injury (AKI) and impacting patient outcomes.

Methods: This retrospective, single-center study included polytrauma victims with an Injury Severity Score (ISS) >25 at a tertiary healthcare center in Dubai.

Results: The incidence of AKI in polytrauma victims is 30.5%, associated with higher Carlson comorbidity index (P=0.021) and ISS (P=0.001). Logistic regression shows a significant relationship between ISS and AKI (odds ratio [OR], 1.191; 95% confidence interval [CI], 1.150–1.233; P<0.05). The main causes of trauma-induced AKI are hemorrhagic shock (P=0.001), need for massive transfusion (P<0.001), rhabdomyolysis (P=0.001), and abdominal compartment syndrome (ACS; P<0.001). On multivariable logistic regression AKI can be predicted by higher ISS (OR, 1.08; 95% CI, 1.00–1.17; P=0.05) and low mixed venous oxygen saturation (OR, 1.13; 95% CI, 1.05–1.22; P<0.001). The development of AKI after polytrauma increases length of stay (LOS)-hospital (P=0.006), LOS-intensive care unit (ICU; P=0.003), need for mechanical ventilation (MV) (P<0.001), ventilator days (P=0.001), and mortality (P<0.001).

Conclusions: After polytrauma, the occurrence of AKI leads to prolonged hospital and ICU stays, increased need for mechanical ventilation, more ventilator days, and a higher mortality rate. AKI could significantly impact their prognosis.

Key Words: acute kidney injury; injury severity score; multiple trauma; renal replacement therapy; rhabdomyolysis

INTRODUCTION

Dubai is one of the most progressive cities in the world. In the last two decades, it has witnessed exponential growth in terms of economics and infrastructure [1]. Dubai is a popular attraction point for expatriates to live and work because it offers high income, low taxes, and
modern lifestyle [1]. Here, the incidents of road traffic accidents (RTAs) are significant due to the availability of cheap oil and high-speed vehicles, diverse population dynamics, and various driving habits [2]. Also in spite of stringent safety measures taken on infrastructure development projects, occasional cases of work-related injuries or fall accidents are seen [3]. Thus, polytrauma due to RTAs, fall accidents, or work-related injuries are not uncommon in Dubai [2,3]. Polytrauma is one of the most common causes of hospital admissions and deaths [4,5]. Kidneys are most vulnerable to dysfunction in polytrauma patients because of various trauma-related pathological factors [4,5]. The reported incidence of acute kidney injury (AKI) in polytrauma victims is 25%–40% [4-6]. Patients with old age, with comorbid conditions like hypertension, diabetes mellitus, ischemic heart disease, and with underlying renal dysfunction are highly vulnerable to developing AKI after polytrauma [7]. The usual causes of AKI in polytrauma patients are hemorrhagic/ hypovolemic shock, rhabdomyolysis, abdominal compartment syndrome (ACS), use of contrast media for various radiological investigations, hypotension associated with surgery/anesthesia and sedation, use of blood and blood product, use of nephrotoxic drugs, and direct injury to kidney, ureter, and bladder [8]. The AKI has a significant impact on patient’s outcomes after polytrauma; it can increase morbidity, mortality, length of stay (LOS) in the hospital, cost of treatment, and intensive care unit (ICU) admission [8].

With this background, we planned an epidemiological study. The main purpose of this study was to determine the incidence, common causes, and predictors of AKI after polytrauma. Also, to know its impact on patient outcomes after polytrauma. Thereby, to upgrade our knowledge, preparedness, and resources to efficiently tackle this one of the vulnerable organ dysfunction counteracting during severe polytrauma.

**MATERIALS AND METHODS**

This is a single-center, retrospective, and observational study done at tertiary health care center (THCC) in the state. The THCC, which is a 762 bedded apex trauma center in the northern part of the state, receives a major portion of polytrauma victims in the state. This study was done after approval from Institutional Scientific Research Ethics Committee (No. DS-REC-04/2022_04). The written informed consent from patients was waived due to the use of retrospective de-identified data in the study.

Polytrauma victims, admitted to THCC between January 1, 2017 and December 31, 2021, were studied. Patients were selected who met all of the following criteria: (1) They were between 18 and 60 years old. (2) They were admitted within 12 hours following severe polytrauma. (3) They had Injury Severity Scores (ISS) of more than 25. (4) They underwent a major surgical procedure and was admitted to ICU. Patients who were excluded who met all of the following criteria: (1) They had ISS less than 25. (2) They were admitted 12 hours after they had polytrauma. (3) They were admitted or resuscitated in the other healthcare facility before admission to the THCC. (4) They had pre-existing renal dysfunction, or they were renal transplant recipients. (5) They had received contrast media more than one time. (6) They were with direct injuries to kidney, ureter, or bladder. (7) They were with more than 5% burns. (8) They were tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA polymerase chain reaction.

After reviewing patient’s electronic medical record (EMR), “epic hyperspace version 2022” (Epic Systems Corp.) data was collected. On a daily basis, the EMR of eligible patients were followed up from the day of admission to the day of discharge or death. The following definitions were used during data collection: (1) For comorbidity, we use Charlson Comorbidity Index (CCI) to quantify the severity of patient comorbidities [9]. (2) A polytrauma victim was defined as any patient who presents with multisystem trauma following RTA, fall from height, or work-related injuries and has an ISS score of more than 25 [10]. (3) For a hypotensive patient requiring noradrenaline support, shock was defined as a dose given that is higher than 0.1 μg/kg/min in order to keep mean blood pressure more than 65 mm Hg. (4) Serum lactate, mixed venous oxygen saturation (ScvO2), and base excess were recorded from on-admission arterial or venous blood gas. (5) Massive transfusion was defined in case of one of the situations: replacement of one entire blood volume within 24 hours, transfusion of >10 units of packed red blood cells (PRBCs) in 24 hours, transfusion of >20 units of PRBCs in 24 hours, transfusion of >4 units of PRBCs in 1 hour when on-going need is foreseeable, or

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**KEY MESSAGES**

- The incidence of acute kidney injury (AKI) after polytrauma is about 30.5%.
- A higher Injury severity score on admission can predict the development of AKI after polytrauma.
replacement of 50% of total blood volume within 3 hours [11]. (6) Use of contrast media was defined as intravenous administration of 120 ml of iohexol (Omnipaque, GE HealthCare) 350 mg/ml for computed tomography polytrauma protocol. (7) Rhabdomyolysis was defined as an increased serum creatinine phosphokinase (CPK) level of more than 6,000 U/L [12]. (8) A major surgical procedure was defined as definitive or damage control surgical procedure done under general anesthesia that satisfied one of the following conditions: (1) It lasted for more than 3 hours of duration. (2) It had an estimated blood loss of more than 1,000 ml. (3) It required perioperative blood transfusion of more than 2 units of PRBC [13]. (9) Nephrototoxic drugs were defined as the use of any of the following drugs: aminoglycosides, amphotericin B, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers, or non-steroidal anti-inflammatory drugs, diuretics. (10) AKI was defined and staged according to KDIGO 2012 clinical practice definition [14]. (11) ACS was defined as an intraabdominal pressure greater than 20 mm Hg associated with new organ dysfunction or failure [15]. (12) Full renal recovery was defined as the occurrence of the patient serum creatinine returning to normal level or baseline [16]. (13) The requirement of renal replacement therapy (RRT) was defined when RRT was done for any of the following indications: volume overload, metabolic acidosis, hyperkalemia, uremia, or persistent/progressive AKI [17]. Continuous venovenous hemodiafiltration mode of RRT is available in our ICU, and that was used in all patients who required RRT.

Initially, we had enrolled a total of 594 patients with ISS more than 25 in the study. But later, we excluded 137 patients. Patients excluded had direct injuries to the kidney, ureter, or bladder diagnosed on computed tomography scan (n=68), had ISS equal to 75 i.e., unsurvivable injuries (n=41), or had developed brain death during the course of management (n=28) (Figure 1). Based on the development of AKI as per KDIGO 2012 clinical practice definition, patients were divided into two groups, viz., the non-AKI group and the AKI group.

The primary objective was to measure the incidence of AKI in polytrauma patients. The secondary objective was to determine risk factors for the development of AKI and its impact on the patient’s LOS in hospital, LOS-ICU, need of mechanical ventilation, and mortality.

**Statistical Analysis**

The data were collected in a Microsoft Excel spreadsheet and analyzed by IBM SPSS ver. 24.0 (IBM Corp.). The categorical variables were represented by frequencies and proportions and analyzed by the Pearson chi-square test. The quantitative variables with normal distribution were represented by the mean and standard deviation and analyzed by the independent samples test. The quantitative variables with skewed distribution were represented by the median and interquartile range and analyzed by the Mann-Whitney U-test. A probability value less than 0.05 (P<0.05) was considered as the point of statistical significance. Finally, to predict the AKI after polytrauma we created either a univariate or multivariate logistic regression model by using the variables with probability values less than 0.05.

**RESULTS**

**Demographic Characters of Polytrauma Victims and Incidence of AKI in Polytrauma**

The demographic characters are shown in Table 1. They were comparable in both groups. Polytrauma was more common among young, male, and expatriate population. The most common mode of polytrauma was RTA. The overall incidence of AKI in polytrauma victims was 30.5%. AKI was common in the patient who had comorbidities. The patient in the AKI group had statistically higher CCI as compared to non-AKI (0.12±0.38 vs. 0.23±0.51, P=0.020). AKI was common in patients who sustained severe injuries as indicated by higher ISS (36.0 [33.0–41.0] vs. 48.0 [37.5–48.0], P=0.001). On the logistic regression model (Figure 2), when the severity of injury (measured by the value of ISS) was compared with the occurrence of AKI, we created a univariate or multivariate logistic regression model by using the variables with probability values less than 0.05.
of AKI. It has shown good regression between them with odds ratio (OR) 1.191 and 95% confidence interval (CI) 1.150–1.233 (P<0.05).

**Causes of the AKI**

The causes of AKI are summarized in the Table 2. There was a significant statistical difference with regards to the presence of shock on admission (yes: 081 [25.9%] vs. 133 [92.4%], no: 232 [74.1%] vs. 11 [7.6%], P=0.001), on admission serum lactate (2.3 [1.4–4.1] vs. 6.6 [4.5–8.9], P=0.001), ScvO2 (75 [75–75] vs. 59 [55–65], P=0.001), and base excess (–4 [2–6] vs. –10 [9–14], P=0.001) between the Non-AKI group to AKI group. High serum lactate, mixed venous oxygen saturation, and base excess in the AKI group indicate that the patients of the AKI group suffered a severe shock. The need of massive transfusion was also high in the AKI group (yes: 45 [14.4%] vs. 131 [91.0%], no: 268 [85.6%] vs. 13 [9.0%, P<0.001). The rhabdomyolysis was more frequent in the AKI group as compared to the non-AKI group (yes: 61 [19.5%] vs. 057 [39.6%], no: 252 [80.5%] vs. 087 [60.4%, P=0.001). However, there was no significant difference between the maximally observed CPK level in both groups (9,306 [73–12,304] vs. 9,768 [7,221–18,775], P=0.368). None of the patients in either group received nephrotoxic drugs. The ACS was reported at a higher rate in the AKI group as compared to the non-AKI group (yes: 6 [1.9%] vs. 23 [16.0%], no: 307 [98.1%] vs. 121 [84.0%], P<0.001).

**Predictors of AKI after Polytrauma**

On the multivariate logistic regression model (Table 3) the main predictors of AKI after polytrauma were higher ISS (OR, 1.08; 95% CI, 1.00–1.17; P=0.05) and low ScvO2 (OR, 1.13; 95% CI, 1.05–1.22; P<0.001).

**The Outcome of Patients after AKI**

The outcome of the patient after AKI is summarized in Table 4. The LOS in the hospital and LOS-ICU in days were higher in a patient who had developed AKI (28 [16–51] vs. 37 [18–73.5], P=0.006; 12 [7–19] vs. 15 [9–23]; P=0.003). A statistically significant proportion of patients who had developed AKI were mechanically ventilated (yes: 255 (81.46%) vs. 138 (95.83%); P<0.001). Also, the patients from the AKI group spent more days on a ventilator (9 [5–16] vs. 7 [12–20], P=0.001). The 28-day mortality was higher in the AKI group (8 [2.6%] vs. 25 [16.7%], P=0.001). Also, the more than 28-day mortality was higher in the AKI group (0 vs. 9 [6.3%], P<0.001).

**Descriptive Statistics of the AKI Group**

The descriptive statistics are summarized in Table 5. A total of 144 (30.5%) out of 457 polytrauma patients developed AKI. Out of these 144 patients, stage 1 AKI patients were 90 (62.5%), stage 2 were 28 (19.44%), stage 3 were 11 (7.6%), and stage 4 were 15 (10.41%). Thirteen patients (9.02%) required RRT. One hundred and twenty patients (83.33%) showed good renal recovery. Thirty-four patients (23.61%) died. None of the patients progressed to chronic renal failure.

**DISCUSSION**

Acute reduction of renal function is defined as AKI [14]. AKI after polytrauma is a common kidney-related complication; the reported incidence of AKI after polytrauma is 25%–40% [4–6]. In our study, the incidence of AKI after polytrauma is found to
Figure 2. Showing logistic regression model illustrating relation between acute kidney injury (AKI) and Injury Severity Score (ISS).

Table 2. Cause of AKI

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-AKI group (n=313)</th>
<th>AKI group (n=144)</th>
<th>P-value</th>
<th>Odds ratio</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shock in 24 hr</td>
<td></td>
<td></td>
<td>0.001(a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>81 (26.4)</td>
<td>133 (92.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>232 (74.6)</td>
<td>11 (7.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On admission lactate</td>
<td>2.3 (1.4–4.1)</td>
<td>6.6 (4.5–8.9)</td>
<td>0.001(b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On admission ScvO(_2)</td>
<td>75 (75–75)</td>
<td>59 (55–65)</td>
<td>0.001(b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On admission base deficient (–)</td>
<td>4 (2–6)</td>
<td>10 (9–14)</td>
<td>0.001(b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Massive transfusion</td>
<td></td>
<td></td>
<td>&lt;0.001(a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>45 (14.4)</td>
<td>131 (91.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>268 (85.6)</td>
<td>13 (9.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td></td>
<td></td>
<td>&lt;0.001(a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>61 (19.5)</td>
<td>57 (39.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>252 (80.5)</td>
<td>87 (60.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum value</td>
<td>9,306 (73–12,304)</td>
<td>9,768 (7,221–18,775)</td>
<td>0.368(b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACS</td>
<td></td>
<td></td>
<td>&lt;0.001(a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6 (1.9)</td>
<td>23 (16.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>307 (98.1)</td>
<td>121 (84.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number (%) or median (interquartile range). AKI: acute kidney injury; ScvO\(_2\): mixed venous oxygen saturation; ACS: abdominal compartment syndrome.

a) Pearson chi-square test; b) Mann-Whitney test.

be 30.5%. Genetic predisposition to the development of end-stage renal disease has been observed [18], and there has been a recent growing interest to define genetics associated with AKI [18, 19]. Because of the abundant expatriate population, Dubai gives a unique opportunity to study genetic predisposition in a specific disease. However in the present study, no differences are found in the incidence of AKI according to patients’ ethnicities (Table 1).

Trauma-induced AKI is more common in a patient with preexisting comorbidities [7]. This finding is confirmed in the present study; the CCI is higher in the AKI group. The usual source of polytrauma-induced AKI is either pre-renal or post-renal cause [8]. Also, the main causes of trauma-induced AKI found are shock, use of massive transfusion, rhabdomyolysis, and ACS. The shock here is hemorrhagic shock; and it is further evident from hyperlactatemia, low ScvO\(_2\), metabolic acidosis, and the higher need of massive transfusion in the AKI group. Other reported causes of trauma-induced AKI are contrast-induced nephropathy [20] and postoperative AKI [21]. Study population had received contrast media only once and had undergone major surgical procedure. The effect of these
### Table 3. Multivariate logistic regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient B</th>
<th>Standard error</th>
<th>z-value</th>
<th>P-value</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charlson comorbidity index</td>
<td>-1.13</td>
<td>0.37</td>
<td>3.03</td>
<td>0.00</td>
<td>0.32</td>
<td>0.15–0.67</td>
</tr>
<tr>
<td>Injury Severity Score on admission</td>
<td>0.08</td>
<td>0.04</td>
<td>1.95</td>
<td>0.05</td>
<td>1.08</td>
<td>1.00–1.17</td>
</tr>
<tr>
<td>Shock in 24 hr</td>
<td>-1.96</td>
<td>0.55</td>
<td>3.56</td>
<td>&lt;0.001</td>
<td>0.14</td>
<td>0.05–0.41</td>
</tr>
<tr>
<td>Lactate</td>
<td>-0.18</td>
<td>0.09</td>
<td>2.05</td>
<td>0.04</td>
<td>0.83</td>
<td>0.70–0.99</td>
</tr>
<tr>
<td>ScvO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0.13</td>
<td>0.04</td>
<td>3.31</td>
<td>&lt;0.001</td>
<td>1.13</td>
<td>1.05–1.22</td>
</tr>
<tr>
<td>Base deficit</td>
<td>0.07</td>
<td>0.06</td>
<td>1.22</td>
<td>0.22</td>
<td>1.07</td>
<td>0.96–1.21</td>
</tr>
<tr>
<td>Massive transfusion</td>
<td>-2.31</td>
<td>0.56</td>
<td>4.13</td>
<td>&lt;0.001</td>
<td>0.10</td>
<td>0.03–0.30</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>-0.76</td>
<td>0.42</td>
<td>1.82</td>
<td>0.07</td>
<td>0.47</td>
<td>0.21–1.06</td>
</tr>
<tr>
<td>ACS</td>
<td>-0.71</td>
<td>0.71</td>
<td>1.00</td>
<td>0.32</td>
<td>0.49</td>
<td>0.12–1.97</td>
</tr>
<tr>
<td>Constant score</td>
<td>-7.56</td>
<td>3.39</td>
<td>2.23</td>
<td>0.03</td>
<td>0.00</td>
<td>-</td>
</tr>
</tbody>
</table>

CI: confidence interval; ScvO<sub>2</sub>: mixed venous oxygen saturation; ACS: abdominal compartment syndrome.

### Table 4. Outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-AKI group (n=313)</th>
<th>AKI group (n=144)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOS in hospital (day)</td>
<td>28 (16–51)</td>
<td>37 (18–74)</td>
<td>0.006&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>LOS in ICU (day)</td>
<td>12 (7–19)</td>
<td>15 (9–23)</td>
<td>0.003&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td></td>
<td></td>
<td>&lt;0.001&lt;sup&gt;H&lt;/sup&gt;</td>
</tr>
<tr>
<td>Yes</td>
<td>255 (81.5)</td>
<td>138 (95.8)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>58 (8.9)</td>
<td>6 (4.2)</td>
<td></td>
</tr>
<tr>
<td>Ventilator day</td>
<td>9 (5–16)</td>
<td>7 (12–20)</td>
<td>0.001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>28-Day mortality</td>
<td>8 (2.6)</td>
<td>25 (17.4)</td>
<td>0.001&lt;sup&gt;H&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

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

AKI: acute kidney injury; LOS: length of stay; ICU: intensive care unit.

<sup>a</sup> Mann-Whitney test; <sup>H</sup> Pearson chi-square test.

### Table 5. Descriptive statistics of AKI group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Stage of AKI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>No. of patient (n=144)</td>
<td>90 (62.5)</td>
</tr>
<tr>
<td>CRRT (n=13)</td>
<td>0</td>
</tr>
<tr>
<td>Full renal recovery (n=120)</td>
<td>82 (91.1)</td>
</tr>
<tr>
<td>CKD/ESRD (n=0)</td>
<td>0</td>
</tr>
<tr>
<td>Mortality (n=34)</td>
<td>11 (12.2)</td>
</tr>
<tr>
<td>28 day</td>
<td>8</td>
</tr>
<tr>
<td>&gt;28 day</td>
<td>3</td>
</tr>
</tbody>
</table>

Values are presented as number (%).

AKI: acute kidney injury; CRRT: renal replacement therapy; CKD: chronic kidney disease; ESRD: end-stage renal disease.

Another important finding is that the ISS is significantly higher in the AKI group compared to the Non-AKI group. There is good logistic regression between the severity of trauma (measured by ISS value) and the probability of developing AKI after trauma. ISS is an indispensable yet easy-to-calculate scoring system used in trauma patients. It is an anatomical score that measures the severity of polytraumas. It is calculated by summing an assigned abbreviated Injury Scale code and score from an internationally recognized dictionary that describes over 2,000 injuries and ranges from 1 (minor injury) to 6 (critical injury). There is a linear correlation between ISS and the severity of trauma [10]. High ISS is associated with hemorrhagic shock and coagulopathy thereby, increasing the two factor is beyond comparison.
Acute kidney injury in polytrauma victims

Wankhade BS, et al. Acute kidney injury in polytrauma victims

The requirement for blood products [22,23]. The eventuality of rhabdomyolysis and ACS after polytrauma is also correlated with high ISS [24-26]. Thus, in the present or earlier studies [4-8], whatever shock, the need for massive transfusion, rhabdomyolysis, and ACS observed are a mere reflection of severe polytrauma as evident from high ISS in the AKI group.

In the present study, patients who had developed trauma-induced AKI, the proportions of stages 1, 2, 3, and 4 of AKI were 62.5%, 19.44%, 7.6%, and 10.41% respectively. The requirement for RRT was observed in 9.02% of patients with AKI. Good renal recovery was observed in 83.33% of patients with AKI. These findings correlate with the metanalysis done by Søvik et al [8]. LOS-hospital, LOS-ICU, the need for mechanical ventilation, days spent on a ventilator, and mortality is significantly higher in the AKI group compared to the non-AKI group. This finding correlates with previous similar studies [4,27].

The merits of this study as compared to previously reported studies [4-6] are our sample size was large, we included severe polytrauma victims (ISS more than 25), we included subjects of diverse ethnicity, and we included subjects with polytrauma due to various causes (RTA, fall, or work-related injuries).

Implications of the study: from the result of this study it is evident that AKI is not uncommon in polytrauma victims and also it can affect the patient outcome after polytrauma. Following implications can be postulated form result of the study. (1) Setup and resources: a health care facility which is routinely managing polytrauma patient should have protocol for early recognition, prevention, and effective management of AKI in polytrauma victims. All the health care providers should keep themselves abreast about this vulnerable organ dysfunction. (2) Resuscitations: all the patient should receive optimal initial resuscitations with fluid or blood product as hemorrhagic shock is a main cause of AKI after trauma. On the other spectrum overzealous fluid resuscitations has its own hazardous like ACS, which is also one of the causes of AKI. So, it is imperative to have balance resuscitations effort which can be best achieved by forming institutional discrete goal directed therapy.

The present study has the following limitations. First, uniformity during initial resuscitation: our study is patient record-based, observational, and retrospective studies. We had not delineated the initial resuscitation protocol in polytrauma patients. Thus, it was difficult to determine whether all patients received uniform resuscitation, which is one of the determining factors for AKI after trauma. Second, outcome variables after AKI: patient’s LOS-hospital, LOS-ICU, need for mechanical ventilation, days spent on a ventilator, and mortality depend on the severity of trauma as indicated by high ISS score [23,28,29]. Similarly, AKI is also more common after severe polytrauma as indicated by the linear relationship between severe polytrauma and a high ISS score. Therefore, it is difficult to determine whether bad outcome variables are caused by AKI alone, or they are a reflection of severe polytrauma.

In conclusion, AKI is common after severe polytrauma. There is a statistically significant logistic regression between the severity of polytrauma and the occurrence of AKI. The incidence of AKI after polytrauma is about 30.5%. AKI is more common in a patient with preexisting comorbidities. The frequent causes of AKI after polytrauma are hemorrhagic shock, massive blood transfusion, rhabdomyolysis, and ACS. Stage 1 AKI is the most common type of AKI after polytrauma. Only a small proportion of patients will require RRT. The outcome of AKI after polytrauma is good, and none of the patients progressed to chronic renal failure. Although the LOS-hospital, LOS-ICU, the need for mechanical ventilation, days spent of mechanical ventilation, and mortality are significantly higher in the AKI group compared to the non-AKI group, this association may be related to more severe injuries in the AKI group. Finally, further prospective studies are needed to know the exact impact of AKI on outcome variables after polytrauma.

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

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ORCID
Bhushan Sudhakar Wankhade https://orcid.org/0000-0002-0288-129X
Zeyad Faoor Alrais https://orcid.org/0000-0002-0249-2673
Ghaya Zeyad Alrais https://orcid.org/0000-0003-3076-3837
Ammar Mohamed Abdel Hadi https://orcid.org/0000-0003-0050-763X
Gopala Arun Kumar Naidu https://orcid.org/0000-0001-7213-4479  
Mohammed Shahid Abbas https://orcid.org/0000-0001-8617-2118  
Ahmed Tarek Youssef Aboul Kheir  
https://orcid.org/0000-0003-0884-7807  
Hasan Hadad  
https://orcid.org/0000-0003-2182-9187  
Sundareswaran Sharma  
https://orcid.org/0000-0001-9083-3687  
Mohammad Sait  
https://orcid.org/0000-0001-6308-6946

AUTHOR CONTRIBUTIONS

Conceptualization: BSW, ZFA, AMAH. Data curation: BSW, GZA, GAKN, MSA, SS, MS. Formal analysis: BSW, ATYAK, HH. Funding acquisition: ZFA. Methodology: BSW, ZFA, AMAH. Project administration: BSW, ZFA. Visualization: ZFA, AMAH. Writing–original draft: BSW, GZA, SS, MS. Writing–review & editing: BSW, GZA, SS, MS.

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Comparison of admission GCS score to admission GCS-P and FOUR scores for prediction of outcomes among patients with traumatic brain injury in the intensive care unit in India

Nishant Agrawal, Shivakumar S Iyer, Vishwanath Patil, Sampada Kulkarni, Jignesh N Shah, Prashant Jedge

Department of Critical Care Medicine, Bharati Vidyapeeth (DTU) Medical College and Hospital, Pune, India

Background: This study aimed to determine the predictive power of the Full Outline of Unresponsiveness (FOUR) score and the Glasgow Coma Scale Pupil (GCS-P) score in determining outcomes for traumatic brain injury (TBI) patients. The Glasgow Outcome Scale (GOS) was used to evaluate patients at 1 month and 6 months after the injury.

Methods: We conducted a 15-month prospective observational study. It included 50 TBI patients admitted to the ICU who met our inclusion criteria. We used Pearson’s correlation coefficient to relate coma scales and outcome measures. The predictive value of these scales was determined using the receiver operating characteristic (ROC) curve, calculating the area under the curve with a 99% confidence interval. All hypotheses were two-tailed, and significance was defined as P<0.01.

Results: In the present study, the GCS-P and FOUR scores among all patients on admission as well as in the subset of patients who were mechanically ventilated were statistically significant and strongly correlated with patient outcomes. The correlation coefficient of the GCS score compared to GCS-P and FOUR scores was higher and statistically significant. The areas under the ROC curve for the GCS, GCS-P, and FOUR scores and the number of computed tomography abnormalities were 0.912, 0.905, 0.937, and 0.324, respectively.

Conclusions: The GCS, GCS-P, and FOUR scores are all excellent predictors with a strong positive linear correlation with final outcome prediction. In particular, the GCS score has the best correlation with final outcome.

Key Words: FOUR score; Glasgow Coma Scale; Glasgow Coma Scale Pupil; Glasgow Outcome Scale; traumatic brain injury

INTRODUCTION

Road traffic injuries are a global phenomenon, causing an annual 1.35 million deaths and resulting in many traumatic brain injuries (TBIs) [1]. The most common cause of death in children <15 years of age and young adults <45 years of age is TBI [2]. In addition to its high
mortality rate, TBI is an important cause of severe morbidity among sufferers [3].

Factors that predict poor outcome in a case of TBI include a Glasgow Coma Scale (GCS) score <8 points, pupillary responsiveness to light, systolic hypotension, concomitant systemic injury, and computed tomography (CT) imaging findings suggestive of hemorrhage [4]. If assessed properly and treated congruously, mild TBI cases (GCS score, 13–15 points) have a good prognosis, and the overall mortality in this group is around 0.1% [5]. Patients with moderate to severe TBI (GCS <13 points) have a much poorer prognosis, with an approximate mortality rate of 30%. The mortality rate of those with severe TBI alone (GCS score ≤8 points) may be as high as 50% [6]. Numerous prognostic indicators like hypotension and hypoxia have been identified to predict death and functional outcome status following TBI [3]. Age is also an independent predictor of functional outcome status and mortality in patients with TBI [7,8].

There are many limitations to the GCS. Local eye trauma and swelling can affect eye responses, and patients who have an endotracheal tube cannot be assessed for verbal response component of GCS [5,6]. Only sparse data are available to suggest that additional examination of pupillary responses has any effect on the overall predictive accuracy of GCS [9-11]. In 2005, Wijdicks and colleagues developed and validated a new coma scale, the Full Outline of Unresponsiveness (FOUR) score, as a suggested replacement for GCS [12]. This tool provides auxiliary information about the functioning of the brainstem and the respiratory drive. It is still, however, unclear which among these two scoring systems has a better predictive value for mortality [12]. Bryan Jennet and Michael Bond published the Glasgow Outcome Scale (GOS) in 1975, 1 year after the GCS was published. This tool is used to assess the patient’s longer-term neurological outcome, functional status, and ability to return to work [13].

The current study aimed to assess the performance of FOUR and Glasgow Coma Scale Pupil (GCS-P) scores to predict the GOS of patients with TBI at the time of hospital discharge or at 1 month and 6 months of follow-up. It also analyzed prediction of GOS by the GCS-P score, age, and CT findings of patients with TBI.

MATERIALS AND METHODS

This study was designed as a prospective observational study. It was performed in the critical care department at a tertiary care university hospital in India. Consecutive patients seen from July 2020 and September 2021 were included in the study. This study was approved by the Ethics Committee (No. BVDUMC/IEC/13, Dated:05/07/2020) and a waiver of written informed consent was obtained as the study was prospective, observational, and non-interventional with data collected anonymously. This study is registered with the Clinical Trials Registry-India (CTRI; registration no. CTRI/2020/09/027837).

Adult patients ≥18 years of age admitted within 24 hours of TBI were included in this study. The inclusion and exclusion criteria are indicated in Figure 1. On admission, history; demographic details; and GCS, GCS-P, and FOUR scores were recorded on the data-collection sheet. Hemodynamic parameters and the presence of hypoxia, hypotension, and concomitant injuries were noted. Admission CT findings, need for and duration of mechanical ventilation, need for surgery, hospital length of stay, and need for tracheostomy were also recorded.

The Pupil Reactivity Score (PRS) summarizes informa-
tion about loss of pupil reactivity to light and is calculated as follows: both pupils unreactive to light, 2 points; one pupil unreactive to light, 1 point; or both pupils reactive to light, 0 points. Then, GCS-P=GCS–PRS. The verbal score for GCS in an intubated patient is calculated as follows: able to talk, 5 points; questionable capacity to talk, 3 points; unresponsive, 1 point.

Eye response, motor response, brainstem reflexes, and respiration are all covered by the FOUR score, which is calculated as follows. Four points are awarded if the eyelids are open or opened, tracking, or blinking on command; the patient can make a thumbs-up, fist, or peace sign; pupil and corneal reflexes are present; and the patient is not intubated, with a regular breathing pattern. Three points are awarded if: the eyelids are open but not tracking; localizing to pain; one pupil is wide and fixed; and the patient is not intubated, with a Cheyne-Stokes breathing pattern. Two points are awarded if the eyelids are closed but open to a loud voice; there is a flexion response to pain; pupil or corneal reflexes are absent; and the patient is not intubated, with irregular breathing. One point is awarded if the eyelids are closed but open to pain; there is an extended response to pain; pupil and corneal reflexes are absent; and the patient breathes above the ventilator rate. Zero points are awarded if the eyelids remain closed with pain; there is no response to pain or generalized myoclonus status; there are absent pupil, corneal, and cough reflexes; and the patient breathes at the ventilator rate or shows apnea.

GOS was assessed at the time of discharge from the hospital or at 1 month from the day of admission, whichever was later, and then again at 6 months through a telephonic survey. The GOS is rated as follows: GOS-1=dead, GOS-2=vegetative state, GOS-3=severe disability, GOS-4=moderate disability, and GOS-5=mild or no disability. The functional outcome was dichotomized (poor/unfavorable outcome versus good/favorable outcome) based on GOS at the time of discharge from the hospital or 1 month after admission, whichever came later, and at 6 months. A poor outcome was defined as GOS of 1–3 points, whereas a good outcome was defined as GOS of 4–5 points.

To record their length of stay, patients were monitored until their release from the hospital. The frequencies (percentages) in each category were calculated for the categorical variables. The near-normality of the distribution for the quantitative variables was evaluated. Mean and standard deviation values were used to summarize the variables with a normal distribution (standard deviation).

Coma scales and outcome measurements were correlated using Pearson’s correlation coefficient, and the area under the receiver operating characteristic curve (AUC) and 99% confidence interval were used to determine the scales’ predictive value. Every hypothesis was two-tailed, and a P<0.01 was deemed statistically significant. The SPSS ver. 22.0 (IBM Corp.) for Windows was used to statistically analyze all data.

RESULTS

Among the 50 patients who were enrolled in this study, the age range was 19–61 years with a mean of 42±13 years, and 74% (n=37) of participants were men (Table 1). Among the enrolled patients (n=50), the mean GCS score was 11.84±3.92, the mean GCS-P score was 11.62±4.33, and the mean FOUR score was 12.98±4.99. Among patients who presented with moderate to severe TBI (n=22), the mean GCS score was 8.05 ±2.88, the mean GCS-P score was 7.55±3.43, and the mean FOUR score was 9.14±4.31 (Table 1).

To determine the predictive value of the GCS, GCS-P, and FOUR scores and the number of CT abnormalities (intracranial hematoma, absent cisterns, and subarachnoid hemorrhage) with regard to mortality, receiver operating characteristic curve analysis was used (Figure 2), and the AUC was calculated. The respective AUCs for the GCS, GCS-P, and FOUR scores and the number of CT abnormalities were 0.912, 0.905, 0.937, and 0.324.

In the present study, the coefficient of correlation of the GCS score compared to the GCS-P and FOUR scores among all 50 patients at admission as well as in the subset of patients who were mechanically ventilated was strongly correlated and statistically significant (Table 2). Of the 43 patients who survived to hospital discharge, 1 had died by 1 month later. The correlation coefficient of GCS score was 0.996 compared to the GCS-P score and was 0.959 for all 50 patients compared to the FOUR score. When considering the ventilated patient subgroup, there was a comparable high correlation. At 1 month after discharge, the correlation coefficients for the 39 patients with a favorable outcome (GOS=4–5 points) were 0.996 for the GCS vs. GCS-P score and 0.936 for the GCS vs. FOUR score, while they were 0.997 and 0.953 for 42 patients, respectively.

At 1 month after discharge, the correlation coefficients for 11 patients with poor outcomes (GOS=1–3 points) were 0.989 for the GCS vs. GCS-P score and 0.930 for the GCS vs. FOUR score, while they were 0.986 and 0.944, respectively, for eight patients. Among the 50 patients, 14 needed mechanical ventilation, 10 needed surgery, and 5 underwent tracheostomy. The
Table 1. Patient demographic details and neurological assessment score

<table>
<thead>
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<th>Variable</th>
<th>Total TBI patients (n=50)</th>
<th>Patients with moderate to severe TBI (n=22)</th>
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<td>Neurological assessment scores on admission and discharge</td>
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<td>4.3±1.5</td>
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</tr>
</tbody>
</table>

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

TBI: traumatic brain injury; GCS: Glasgow Coma Scale; GCS-P: Glasgow Coma Scale Pupil; FOUR: Full Outline of Unresponsiveness; GOS: Glasgow Outcome Scale.

Figure 2. Receiver operating characteristic curve of Glasgow Coma Scale (GCS), Glasgow Coma Scale Pupil (GCS-P), Full Outline of Unresponsiveness (FOUR) scores, and number of computed tomography (CT) abnormalities.

DISCUSSION

Reported in 1974 by Teasdale and Jennet, the GCS remains the gold-standard method of assessing neurological status in patients with TBI [5]. However, researchers have since focused on the development of more accurate tools, which include the FOUR score and the GCS-P score. Hence, this study was conducted to compare FOUR and GCS-P scores in patients with TBI to predict their outcomes in the intensive care unit (ICU).

Our study was performed in patients aged ≥18 years admitted to the ICU with TBI. Some studies performed by various researchers such as Baratloo et al. [14], Furman et al. [15], Gheilikhkhani et al. [16], Gorji et al. [17], Hossein et al. [18], Jalali and Rezaei [19], Kafle et al. [20], McNett et al. [21], Nair et al. [22], Nyam et al. [23], Okasha et al. [24], Sadaka et al. [25], Saika et al. [26], and Sepahvand et al. [27] exclusively enrolled TBI patients, whereas other studies by Bayraktar et al. [28], Bruno et al. [29], Eken et al. [30], Gujjar et al. [31], Khanal et al. [32], Ramazani and Hosseini [33], Wolf et al. [34], and Temiz et al. [35] included subjects with medical and/or neurological con-
Our study sample consisted mainly of young men with a mean age of 42.08 years, and 94% of them were <60 years of age. Our findings are consistent with those reported by Jalali and Rezaei [19], in that the mean age of their sample was 41±18 years, and 77.9% of them were men. Similarly, other studies by Hossein et al. [18], Kafle et al. [20], Saika et al. [26], and Temiz et al. [35] reported relatively lower mean ages of 34±2, 39±18, 38±16, and 47±20 years, respectively. In contrast, in their study performed at Selçuk University, Bayraktar et al. [28] enrolled 79 patients admitted to the ICU whose mean age was 53±14 years, which is high compared to our findings.

In the present study of 50 samples, the various comorbidities reported were diabetes (14%), hypertension (4%), and ischemic heart disease (2%), and a few patients had multiple comorbidities like diabetes and hypertension (4%) or diabetes, hypertension, and IHD (2%). A diagnostic accuracy study comparing GCS and FOUR scores in predicting mortality in trauma patients by Ghelichkhani et al. [16] at Tehran University of Medical Sciences in Iran reported comorbidity trends consistent with our study findings.

In the present study, the mean GCS score reported on admission was 11.84±3.92 points, while the mean FOUR score was 12.98±4.99 points and the mean GCS-P score was 11.62±4.33 points. The mean scores of GOS at 1 month and 6 months after discharge were 4.2±1.46 and 4.32±1.48 points, respectively. These findings are consistent with those of the study by Kafle et al. [20] of 122 head injury patients attending Tribhuvan University Teaching Hospital in Nepal, which reported a mean GCS score of 10.43±2.5 points and a mean FOUR score of 12.15±3.15 points.

Existing studies have shown that AUCs for prediction of mortality for GCS and FOUR scores vary between 0.72 and 0.96 in published studies, and the scores correlated well with each other (Table 3). Studies performed in different settings and differences in the skill level of health care workers in assessing comatose patients could contribute to this variation. None of the available studies to the best of our knowledge have directly compared and correlated the GCS-P and FOUR scores.

The GCS-P score adds evaluation of the pupil, which is very subjective and may not be more precise than the GCS score. A more precise assessment of the size of the pupil by pupillometry may help to predict the outcome more accurately than the GCS-P score alone. Automated infrared pupillometry using a handheld device will allow more objective and quantitative
measurement of pupillary function compared to a visual inspection. Further assessment of brainstem reflexes and respiratory pattern, as seen in the FOUR score, adds complexity at bedside.

The strengths of this study include supplementation of limited studies comparing the GCS, GCS-P, and FOUR scores. Hence, it is a unique study that investigates the correlation between GCS, GCS-P, and FOUR scores at admission with the GOS at both 1 month and 6 months after discharge. The follow-up was performed meticulously, and there was no patient lost to follow-up. In a sample of patients with moderate-to-severe TBI, the correlations between the GCS, GCS-P, and FOUR scores and the GOS were examined individually.

The limitations of the study are as follows. Our sample size was only 50 patients, as cases of road traffic accidents with TBI were limited in number due to the coronavirus disease 2019 pandemic, and patients who were treated elsewhere were excluded from the study along with those with chronic organ failures, chronic degenerative neuro-illness, or who had already received sedative drugs. Despite the lack of significant difference in the correlation between the scores of patients in our study with moderate-to-severe TBI, a larger investigation focused on such a subset of patients is necessary. Among the cohort of patients who visited our hospital, few had moderate-to-severe TBI during the study period, and enrolling more patients with this condition might change the end result. Admission GCS scores may vary depending on how quickly the patients present to the hospital. Assessing GCS, GCS-P, and FOUR scores just prior to intubation as well as at the time of admission may ensure a more accurate correlation with the final outcome and should be studied further. Finally, the use of pupillometry might have improved the accuracy of our measurements.

In this prospective observational study, the GCS-P and FOUR scores did not show any significant difference in the prediction of outcomes among patients with mild to moderate TBI. We also conclude that the gold-standard GCS score compared to the GCS-P and FOUR scores shows the best correlation with outcome in patients with mild to moderate TBI. It remains to be seen whether the GCS-P score or the FOUR score will perform better in a cohort of severe TBI patients and when an objective assessment of the pupils is conducted with a pupillometer.

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ORCID
Nishant Agrawal https://orcid.org/0000-0003-4071-5142
Shivakumar S Iyer https://orcid.org/0000-0001-5814-2691
Vishwanath Patil https://orcid.org/0000-0002-0103-2210
Sampada Kulkarni https://orcid.org/0000-0002-1445-747X
Jignesh N Shah https://orcid.org/0000-0002-8812-8791
Prashant Jedge https://orcid.org/0000-0002-9655-159X

AUTHOR CONTRIBUTIONS
Conceptualization: JNS. Methodology: JNS, PJ. Formal analysis: NA. Data curation: NA. Visualization: VP, JNS. Project administration: VP, SK, JNS, PJ. Writing—original draft: NA. Writing—review & editing: SSI, VP, SK, JNS, PJ.

REFERENCES
Comment on “Risk factors for intensive care unit readmission after lung transplantation: a retrospective cohort study”

Maida Qazi, Mahnoor Amin

Dow University of Health Sciences, Karachi, Pakistan

Dear Editor:

“Risk factors for intensive care unit readmission after lung transplantation: a retrospective cohort study” by Kim et al. [1] provided exceptional information regarding the increased risk of intensive care unit (ICU) readmission after initial ICU discharge during index hospitalization following lung transplantation by illuminating associated factors. In-depth details support the article as a result of the author’s remarkable knowledge of their respective disciplines. Sequential Organ Failure Assessment (SOFA) score is independently associated with increased risk of ICU readmission after lung transplant, and as such is a common measure for evaluating clinical condition of critically ill patients and their response to treatment. We concur with the article’s conclusion that ICU readmission can be reduced and patient survival can be improved through careful optimization by managing rigorous postsurgical infections. However, we believe that this research should have included a few additional points that could have enhanced the study’s value.

First, this article lacks preoperative and postoperative status information for the patients and the respective hospital policies regarding care and assessment of lung transplantation patients. According to a previous study, pulmonary test function, assessment of severity of functional dyspnea through modified Medical Research Council Dyspnea scale, muscle strength measurements using a digital dynamometer, Beck Depression Inventory for evaluating psychological state, short form-36 for evaluating quality of life and a 2-day supervised exercise program should be used to appraise the preoperative status of end-stage lung disease patients [2]. A systematic review revealed that in the early postoperative phase after lung transplantation, there is a considerable reduction in quadriceps muscle weakness due to critical myopathy, impaired skeletal muscle oxidative capacity, and local wound complications due to continuous motion in the thoracic region or old age factors. One study of 700 lung transplant recipients found a 9.2% incidence of neurological complications including stroke and metabolic encephalopathy in the first 2 weeks posttransplantation. Also, a retrospective study revealed the 90-day mortality rate in patients with neurologic complications after lung transplantation to be 15% and only 4% among recipients who did not develop such complications [3].

Moreover, the study’s retrospective nature raises several problems due to the possibility of recollection bias and inaccurate patient reporting. Also, a single-center study may be affect-
ed by bias due to differences in health, socioeconomic, and environmental variables and constrained statistical analysis. Furthermore, details are required regarding the length of hospital stay after lung transplantation. A study in 2017 showed a notable proportion of patients had a prolonged length of stay after lung transplantation, with donor-, recipient- and procedure-related factors being independent predictors of such results, including lung allocation score, functional status, serum albumin and the need for extracorporeal membrane oxygenation; patients with a prolonged length of stay have higher risk of death 1 or 5 years of lung transplantation [4].

Additionally, along with confounding factors including age and other comorbidities for lung transplantation, details about hospital policies regarding nosocomial infections such as Pseudomonas aeruginosa, *Staphylococcus aureus* and *Mycoplasma hominis* causing wound infections and also hospital acquired pathogens like methicillin-resistant *S. aureus* and various bacterial infections causing cholangitis and anastomotic leaks should be stated in this study [3]. Although factors related to nosocomial infections vary across different regions and hospitals, they should still be taken in consideration. Moreover, some information regarding factors associated with discharge frailty following lung transplantation should also have been incorporated into the article. In one study, almost 80% of older adult survivors of a medical ICU admission were frail at discharge. The factors associated with discharge frailty were female sex, pulmonary fibrosis, and acute kidney injury. In addition to this, another study evaluated the association of an intensive outpatient physical therapy program with improvement in frailty and frailty scores among selected frail patients after lung transplantation [5].

**CONFLICT OF INTEREST**

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**ORCID**

Qazi M https://orcid.org/0000-0002-6902-0152
Mahnoor A https://orcid.org/0000-0001-9395-4521

**AUTHOR CONTRIBUTIONS**

Conceptualization: MQ. Data curation: MQ. Formal analysis: MQ. Methodology: MQ. Visualization: MQ. Writing–original draft: all authors. Writing–review & editing: MA.

**REFERENCES**

We appreciate Qazi and Amin [1] for their interest in our study [2]. We agree that a better prognosis for lung transplantation (LT) patients requires consideration and management of various perioperative factors. As noted in the Introduction section, we focused on the postoperative state of LT patients, showing substantial change due to surgery, rather than their preoperative condition. We assessed the patients’ baseline pulmonary function, educational level (as a proxy for socioeconomic status), and Eastern Cooperative Oncology Group performance status (a comprehensive measure of overall health status that incorporates the modified Medical Research Council dyspnea scale) to obtain a more complete understanding of their condition. However, we did not examine and document the patients’ muscle strength or emotional state between 2012 and 2017. We have recently evaluated and optimized measurement of patients’ physical and mental status with patient-centered techniques before and after surgery, as we recognize their crucial impact on prognosis [3].

Considering the possibility of various complications following LT, we acknowledge the importance of close observation and meticulous management, in conjunction with rehabilitation protocols. Since the introduction of LT, various rehabilitation programs have been implemented and refined. However, at the time of study performance, such programs were not fully established, and there were numerous missing data points regarding patients’ respiratory and physical status, which posed a challenge for our retrospective research.

Nevertheless, we suggest that major postoperative complications occurring early after LT, which can significantly affect recovery trajectory, have been identified through causes of intensive care unit (ICU) readmission or in-hospital mortality, as presented in Figures 2 and 3 of our article [2]. Except for rejection, immunosuppressant-related infections, and rehabilitation issues, individualized measures for specific complications should be taken following LT, rather than relying solely on general treatment protocols for LT patients.

LT recipients in our study were managed according to the established protocol, including immunosuppressive therapy with administration of tacrolimus, mycophenolate mofetil, and steroids. Antibiotics such as teicoplanin or vancomycin and cefepime were administered for 5 days after surgery to prevent bacterial infection. Ganciclovir, later switched to oral valganciclovir, to prevent cytomegalovirus infection and itraconazole to avoid fungal infec-
tion were given for six months. In addition, trimethoprim/sulfamethoxazole was given to prevent Pneumocystis jirovecii infection. Our study would have been more comprehensive if we had included these aspects. However, our protocol cannot be generalized to LT recipients in other medical facilities due to potential differences in epidemiology and antibiotic resistance patterns.

Numerous studies have identified hospital length of stay (LOS) and unplanned rehospitalization as potential predictive factors for mid- and long-term outcomes following LT [4,5]. However, few studies have examined the prognostic factors during the early postoperative period after LT. We believed identifying and modifying the factors that impacted early outcomes following LT should be a priority to improve mid- to long-term outcomes. Therefore, we aimed to investigate the risk factors for ICU readmission during the initial hospitalization period following LT, rather than considering the entire hospital LOS or discharge frailty. Upon reviewing our study population, patients who were readmitted to the ICU had a significantly longer hospital LOS after surgery (32 days [23–45] vs. 107 days [61–151], P<0.001). This implies that mitigating ICU readmission via early risk factor modification may reduce hospital LOS and ultimately improve patient prognosis.

Last, we also mentioned that ours is a retrospective study conducted on a relatively small number of patients at a single center and is inherently limited in its research design. Therefore, we advocate for additional large-scale, prospective, multicenter studies or artificial intelligence models using extensive data for predicting the prognoses of LT recipients.

CONFLICT OF INTEREST

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

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ORCID

Hye-Bin Kim https://orcid.org/0000-0003-3108-8693
Sungwon Na https://orcid.org/0000-0002-1170-8042
Hyo Chae Paik https://orcid.org/0000-0001-9309-8235
Hyeji Joo https://orcid.org/0000-0003-4194-5820
Jeongmin Kim https://orcid.org/0000-0002-0468-8012

AUTHOR CONTRIBUTIONS

Conceptualization: HBK, JK. Formal analysis: HBK. Data curation: HBK. Writing–original draft: HBK. Writing–review & editing: SN, HCP, HJ, JK.

REFERENCES

Dear Editor:

Mortality due to sepsis has decreased with dissemination of the sepsis bundle. To successfully manage sepsis, it is essential to diagnose the source of infection, administer antibiotics, surgically treat if needed, and concurrently resuscitate the patient as soon as possible [1]. However, even when a patient is adequately managed, treatment can fail if the culprit pathogen cannot be identified. Such cases can require extensive analysis including rare pathogens. Invasive fungal disease (IFD) is suspected as a source of sepsis in immunocompromised hosts, and conventional risk factors are well established. Neutropenia, hematopoietic stem cell or solid organ transplantation, high-dose corticosteroid use, and immunosuppressant use are proven risk factors [1]. However, there have been cases of suspected IFD in patients with no conventional risk factors. Here, we present an interesting case of community-acquired pneumonia and septic shock in which invasive pulmonary aspergillosis was considered as the primary pathogenesis. The patient was anonymized, and the Institutional Review Board of Soonchunhyang University Bucheon Hospital approved this study (No. 2023-02-018). Because of the retrospective review of a discharged patient, the need for informed consent was waived.

An 85-year-old man with a history of carotid artery stenosis, hyperlipidemia, chronic kidney disease, and dementia was admitted to the intensive care unit (ICU) because of sputum produced 1 day prior and worsening dyspnea on the visit day. Upon admission, the patient was drowsy, with blood pressure 69/37 mm Hg, heart rate 75 beats/min, respiratory rate 22 beats/min, body temperature 36.9 °C, and pulse oxygen saturation 60% at room air. Coarse breath sounds with crackles were heard in both lung fields. Concurrent with mechanical ventilation, adequate intravenous fluid and norepinephrine were administered. The initial serum lactate level was elevated to 2.5 mmol/L. Chest radiograph showed increased opacities mainly in the right lower lung field (Figure 1A). Chest computed tomography revealed multifocal nodules with surrounding ground-glass opacities (GGOs), the “halo sign” in underlying emphysematous lungs, and extensive consolidation with GGO in both lower lobes (Figure 2A and B). The initial white blood cell and absolute neutrophil counts were 3,110/μl and 2,430/μl, which increased to 8,430/μl and 6,830/μl on the second day, respectively. Non-specific erythematous bronchial mucosa with a large amount of thick, purulent sputum was observed on bronchoscopy, and bronchial lavage and culture were performed. Serum high-sensitivity C-reactive protein (hs-CRP) and procalcitonin levels were 16.47
Figure 1. (A) The initial chest radiograph shows increased opacities, mainly in the right lower lung field. (B) The last chest radiograph on the 74th day of admission reveals decreased opacities compared to (A).

Figure 2. (A) The coronal view of initial chest computed tomography (CT) shows bilateral multifocal nodules with surrounding ground-glass opacities (GGOs), the “Halo sign” (black arrows), and centrilobular emphysema (white arrowheads) in both lungs. (B) Axial images of the same CT scan reveal multiple nodules with surrounding GGO (black arrows in the above row) in both upper lobes and extensive consolidation with GGO (black arrows in the bottom row) in both lower lobes. (C) The follow-up axial CT images show aggravated nodular consolidations in the upper and lower lobes on the 13th day of admission. (D) The second follow-up axial chest CT images show partial improvement of nodular consolidations in the whole lung fields on the 45th day of admission.

mg/dl and 20.9 ng/ml, respectively. The broad-spectrum antibacterial agent cefepime was infused immediately. During the first 5 days, the blood platelet count decreased markedly from 103,000 to 65,000/µl; serum creatinine level increased from 1.7 to 2.0 mg/dl; and serum hs-CRP and procalcitonin levels increased to 18.07 mg/dl and 55.0 ng/ml, respectively. The initial bronchoscopic culture and respiratory virus multiplex tests showed negative results, except the galacto-
mannan (GM) antigen level from bronchoscopic washing was elevated at 1.5. The serum GM antigen level was also elevated at 4.99 (Figure 3). Blood beta-D-glucan (BDG) level peaked at greater than 1,000.0 pg/ml. With suspicion of invasive aspergillosis, oral voriconazole was added on the third day of admission. The patient was not at high risk for multidrug-resistant organism infection related to recent exposure to antimicrobial drugs or hospital admission and was not at high risk for opportunistic infection due to immunosuppression. Ten days later, given that the hs-CRP level was still high at 16.06 mg/dl and the follow-up chest CT images revealed aggravation of nodular consolidations, oral voriconazole was replaced with intravenous liposomal Amphotericin B (Figure 2C). The hs-CRP level finally improved to 3.80 mg/dl 1 week after start of intravenous liposomal Amphotericin B. Finally, Aspergillus fumigatus was cultured on the 33rd day from the endotracheal aspirate sample collected on the 26th day of intensive care. The patient was weaned from the mechanical ventilator on the 40th day of ICU admission in the tracheostomy state and discharged from the ICU after 45 days of intensive care. The follow-up radiograph and CT images showed partial improvement of nodular consolidations (Figure 1B and 2D).

IFD may have a poor prognosis without a timely diagnosis, especially in non-neutropenic patients [2]. Prohaska et al. [3] reported a case of fatal acute respiratory distress syndrome with undiagnosed IFD, in which Mucor and Aspergillus mycelium were identified at autopsy. The patient had no conventional risk factor and died with an enigmatic course despite full coverage of the identified bacteria.

The diagnostic method of choice for proven invasive aspergillosis is biopsy. However, transtheaneous lung biopsy is associated with risk of iatrogenic pneumothorax and air embolism, especially in patients on mechanical ventilators. More noninvasive diagnostic tools are needed for IFD, especially for critically ill patients. In the latest statement for IFD in 2021, probable invasive aspergillosis was defined as either the presence of Aspergillus species or GM positivity in the

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**Figure 3.** Serum invasive fungal markers of galactomannan antigen (GM) and beta-D-glucan (BDG) levels were initially high but decreased upon treatment, with a persistent and intractable disease course.
serum and/or bronchoalveolar fluid, plus a supporting radiological finding and a supporting host factor. Among the host factors, chronic respiratory airway abnormality and severe viral pneumonia were included [4]. Some other risk factors for IFD have been proposed, including diabetes mellitus, alcoholism, malnutrition, and critical illness [2].

At first, our patient seemed to have no relevant risk factor for invasive aspergillosis, except slight emphysematous change in both lungs on chest CT. However, his serum and bronchial washing GM were positive, and the serum level of BDG [5], another fungal marker, was increased. Further, the radiologic findings were consistent with invasive aspergillosis, e.g., the “halo sign,” contrary to most non-neutropenic patients showing non-specific results [2]. Finally, we diagnosed the patient with probable invasive aspergillosis and prescribed antifungal treatment.

In critically ill patients who are unresponsive despite proper management, IFD, such as invasive aspergillosis, should be suspected because of its high mortality, even in patients without non-conventional risk factors. It is helpful to assess serum invasive fungal markers such as GM and BDG and nodular consolidations with surrounding GGO on CT images, instead of obtaining a more invasive lung biopsy. Non-conventional risk factors and non-invasive diagnosis of IFD should be investigated further and are considered in our current practice.

CONFLICT OF INTEREST

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

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ORCID

Kyung Eun Shin https://orcid.org/0000-0003-2373-4704
Shinhee Park https://orcid.org/0000-0002-5783-6795
Ae-Rin Baek https://orcid.org/0000-0003-1350-610X

AUTHOR CONTRIBUTIONS

Conceptualization: ARB. Data curation: KES, ARB. Funding acquisition: ARB. Methodology: all authors. Project administration: ARB. Visualization: KES, ARB. Writing—original draft: KES, ARB. Writing—review & editing: all authors.

REFERENCES

Extracorporeal cardiopulmonary resuscitation for out-of-hospital cardiac arrest and in-hospital cardiac arrest with return of spontaneous circulation: be careful when comparing apples to oranges

Hwa Jin Cho¹,², In Seok Jeong²,³, Jan Bělohlávek⁴

¹Division of Pediatric Cardiology and Cardiac Intensive Care, Department of Pediatrics, Chonnam National University Children’s Hospital and Chonnam National University Medical School, Gwangju, Korea
²Extracorporeal Circulation Research Team, Chonnam National University Hospital, Gwangju, Korea
³Department of Thoracic and Cardiovascular Surgery, Chonnam National University Hospital and Chonnam National University Medical School, Gwangju, Korea
⁴2nd Department of Medicine-Department of Cardiovascular Medicine, First Faculty of Medicine and Charles University and General University Hospital, Prague, Liberec, Czech Republic

Extracorporeal membrane oxygenation (ECMO) is a resource-intensive and costly form of life support that is increasingly being applied to complex patients with cardiac arrest, now referred to as extracorporeal cardiopulmonary resuscitation (ECPR) [1]. The decision to use ECPR in patients with cardiac arrest is still made on a case-by-case basis, but initiation criteria vary among clinicians, institutions, and regions. Neurological outcomes after ECPR are among the most important outcomes, and a tool that is simple, quick, and utilizes readily available clinical information to predict the likelihood of various neurological outcomes could be extremely beneficial in the care of potential ECPR candidates [2]. However, current tools for predicting neurologic outcomes lack sufficient evidence for use in individual patients and need to be validated in patients with cardiac arrest [3-6].

In this issue of Acute and Critical Care, Lee et al. [7] investigated the ability of the respiratory quotient (RQ) measured within the first 24 hours after ECPR to predict neurological outcomes. The study included a relatively large and mixed population of in-hospital and out-of-hospital cardiac arrest (IHCA and OHCA) ECPR cases (a total of 155 participants) from a tertiary referral hospital in South Korea, spanning a period of 17 years. The research incorporated clinical variables collected within 24 hours following ECPR. Although the RQ was higher than the normal value in ECPR patients, it was not found to be associated with poor neurological outcomes.

The primary strengths of this study include its relatively large cohort of ECPR patients, the simplicity and ease of collecting variables, the inclusion of any patient on ECPR regardless of indication, and the more detailed data on RQ, which has been studied in many other fields, but not in this context. The significant risk factors associated with poor neurological outcomes in this study were age, CPR to pump-on time, and serum lactate levels above 7.1 mmol/L. Interestingly, initial lactate levels were lower than those reported in the largest randomized population to date, which may reflect the high percentage of patients who achieved return of spontaneous circulation before ECMO cannulation [3]. The authors hypothesized that
patients with ECPR and poor neurological outcomes would tend to be older, have longer CPR to pump-on times, have a higher proportion of OHCAs, have more comorbidities such as hypertension and coronary artery disease, and have higher initial Sequential Organ Failure Assessment (SOFA) scores. However, this may not be true for different types of ECPR populations, particularly when comparing OHCA and IHCA cases. Among hypoxia parameters (e.g., RQ, venous-arterial difference in CO₂ tension, and serum lactate), lactate had the highest predictive power, which may warrant further discussion. The authors correctly emphasized that RQ was inferior to lactate in predicting poor neurological outcomes in patients who received ECPR in this study. They explained this finding by noting that blood gas measurements may be influenced by sweep gas and ECMO flow rates. The study incorporated data gathered over an extended period and did not include a group of patients who received support without ECMO, which may limit the study's power. Additional limitations encompass selection bias, the retrospective observational study design, and the exclusion of other centers from the study. A notably high percentage of patients (approximately 60%) experienced poor neurological outcomes, corroborating the earlier observation that this population does not constitute a true ECPR cohort, defined as those receiving implantation during ongoing chest compressions. As a result, the findings of this study may not be directly applicable to all ECPR patients.

The study by Lee et al. [7] identified several risk factors associated with poor neurological outcomes in patients undergoing ECPR, regardless of the underlying disease. Although the authors investigated a relatively novel variable (RQ) in ECPR patients, it was found to be less predictive than serum lactate levels. Nevertheless, the authors should be commended for providing a valuable stepping stone for predicting neurological outcomes, as their work helps to objectively quantify the risks and benefits of initiating ECMO versus continuing conventional care for individual patients.

**CONFLICT OF INTEREST**

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**ORCID**

Hwa Jin Cho https://orcid.org/0000-0002-2458-8529
In Seok Jeong https://orcid.org/0000-0002-2249-0667
Jan Bělohlávek https://orcid.org/0000-0001-9455-9224

**AUTHOR CONTRIBUTIONS**

Conceptualization: all authors. Writing–original draft: HJC. Writing–review & editing: all authors.

**REFERENCES**

The collection of air in the cranial cavity is called pneumocephalus. Although simple pneumocephalus is a benign condition, accompanying increased intracranial pressure can produce a life-threatening condition comparable to tension pneumothorax, which is termed tension pneumocephalus. We report a case of tension pneumocephalus after drainage of a cerebrospinal fluid hygroma. The tension pneumocephalus was treated with decompression craniotomy, but the patient later died due to the complications related to critical care. Traumatic brain injury and neurosurgical intervention are the most common causes of pneumocephalus. Pneumocephalus and tension pneumocephalus are neurosurgical emergencies, and anesthetics and intensive care management like the use of nitrous oxide during anesthesia and positive pressure ventilation have important implications in their development and progress. Clinically, patients can present with various nonspecific neurological manifestations that are indistinguishable from those of a primary neurological condition. If the diagnosis is questionable, patients should be investigated using computed tomography of the brain. Immediate neurosurgical consultation with decompression is the treatment of choice.

Key Words: decompressive craniectomy; nitrous oxide; positive-pressure respiration; pneumocephalus
of the femur. The postoperative course was uneventful. On the 7th postoperative day; however, she developed right-sided hemiparesis and altered mental status. The Glasgow coma scale (GCS) was 10/15 (E4, V1, M5). Noncontrast computed tomography (NCCT) of the brain suggested bilateral cerebrospinal fluid (CSF) hygroma more strongly affecting the left side than the right side at the cerebral convexity (Figure 1). She was referred to a neurosurgeon and subsequently underwent a left parietal Burr hole and evacuation of CSF hygroma under general anesthesia. She was extubated in the postoperative period and remained in an intensive care unit (ICU) for neuro observation. Postoperatively, her GCS was 15/15 (E4, V5, M6), but she had persistent right-sided hemiparesis, which was similar to her preoperative state. Six hours postoperatively, she developed generalized tonic-clonic seizures, and her GCS dropped to 5/15 (E1, V1, M3). She underwent immediate intubation to secure her airway. She was sedated with a continuous infusion of fentanyl and midazolam, and she was connected to mechanical ventilation. She also received antiepileptic levetiracetam. Another NCCT of the brain revealed near-complete evacuation of the bilateral CSF hygroma and development of the classic “Mount Fuji” sign, indicating the formation of TPC (Figure 2). Her management included maintenance in a flat position in bed, 100% oxygen, sedation, an antiepileptic, and other brain-protective measures. She underwent immediately surgery, and a neurosurgeon performed left frontoparietal decompressive craniectomy under general anesthesia. Postoperatively, she was kept in the ICU under sedation. On the second postoperative day, a repeat NCCT of the brain showed near-complete resolution of the pneumocephalus. Her sedation was stopped, but her GCS did not improve beyond 9/15 (E4, V1, M4). On the 7th postoperative day, she underwent a tracheotomy for low GCS. Unfortunately, the patient developed other complications associated with her critical illness: ventilator-associated pneumonia, sepsis, acute kidney injury, and multi-organ failure. Finally, she succumbed to death on the 25th postoperative day. Because the patient was deceased, we obtained consent from her son for publication of this case report. This case report was approved by the head of the ICU of our hospital.

DISCUSSION

Pneumocephalus or pneumatocele is defined as the presence

![Figure 1. Computed tomography of the brain showing cerebrospinal hygroma left side more than right side at cerebral convexities.](image1)

![Figure 2. Computed tomography of the brain showing classical "Mount Fuji" sign indicating the development of tension pneumocephalus.](image2)
of gas within any intracranial compartment of the cranial vault: intraventricular, intraparenchymal, subarachnoid, subdural, or epidural. The term “pneumocephalus” was described first by Wolff in 1914 [2]. In 1962, Kessler and Stern [3] reported a case of pneumocephalus that caused brain herniation leading to rapid deterioration and death. They described the term “tension pneumocephalus,” which is the same as tension pneumothorax and requires immediate intervention.

The most common cause of pneumocephalus is traumatic head injury. The reported incidence of pneumocephalus after a head injury is 0.5% to 1% [4]. Other common causes of pneumocephalus include (1) craniofacial trauma especially involving the skull base [5]; (2) intra- or extracranial neurosurgical an intervention like drainage of subdural hemorrhage, shunt surgeries, or CSF drainage [5]; (3) spinal or epidural injections [5]; (4) otorhinolaryngological procedures [5]; (5) infections involving the brain or middle ear such as brain abscess, encephalitis, meningitis, and otitis [5]; (6) brain tumors [5]; (7) positive pressure ventilation, either invasive or non-invasive [6]; (8) nitrous oxide as an anesthetic during anesthesia [7]; (9) air travel (a small pneumocephalus can grow due to pressure changes at high altitude) [5]; (10) barotrauma, hyperbaric oxygen therapy [5]; and (11) radiotherapy to the cranium [5].

Several mechanisms have been postulated in the pathophysiology of pneumocephalus. (1) The inverted soda bottle effect occurs when CSF is lost due to any cause. This loss will decrease the ICP, and air will be sucked into the cranial cavity to replace the lost volume of CSF [5]. (2) The ball valve mechanism occurs when the extra-cranial pressure is greater than the ICP (e.g., sneezing, coughing, and straining), and air enters the cranial cavity. The affected intracranial structure seals the entry site, and the flow of air is sparse [5]. This mechanism is responsible for pneumocephalus associated with positive pressure ventilation [5,6]. (3) During epidural injections, pneumocephalus mainly develops if a loss of resistance technique is used to identify the epidural space [5]. The air can enter the meninges due to accidental injection, inadvertent dural puncture, or pressure differences between the intraventricular/cisternal space and atmosphere [5]. (4) During anesthesia, pneumocephalus can develop due to the use of nitrous oxide during anesthesia. The blood-gas partition coefficient of nitrous oxide is 34 times greater than that of nitrogen, allowing nitrous oxide to diffuse into the cranial vault faster than nitrogen or air [7]. (5) During air travel, a small pneumocephalus can increase in size and can lead to TPC. Boyle’s law states that if the temperature remains fixed in a confined space like the cranial cavity, the absolute pressure and volume are inversely proportional. Thus, when absolute pressure decreases (e.g., during a flight), the volume of air increases proportionally [5].

The clinical features of pneumocephalus and TPC are similar and nonspecific. The most common symptoms include nausea, vomiting, headache, altered mental status, and convulsions [5,8]. Neurological findings include nuchal rigidity, photophobia, and focal neurological deficit [5,8]. In cases of TPC, clinical deterioration is due to increased ICP and the Cushing reflex [8]. The patient can present with bradycardia, hypertension, or even cardiac arrest [8]. If the patient has an ICP monitoring device, it can show a high reading [8]. When there is doubt between simple pneumocephalus and TPC, the patient should be investigated, as simple pneumocephalus does not usually require decompressive surgery [8].

Pneumocephalus can be investigated by plain X-ray of the skull and computed tomography (CT) of the brain [5]. Although X-ray of the skull can detect a large pneumocephalus, it is seldom used with the advancement of CT; CT of the brain is the investigation of choice [9]. When pneumocephalus is detected on brain CT, the patient should be investigated for a skull base fracture or CSF leak [1]. Radiological signs described for diagnosis of pneumocephalus/TPC are the peaking sign, Mount Fuji sign, and air bubble sign [5,9]. The peaking sign is bilateral compression of the frontal lobes caused by trapped air in the subdural space. This sign demonstrates no separation of the frontal lobes and is more common in pneumocephalus than in TPC [5,9]. The Mount Fuji sign is bilateral compression and separation of the frontal lobes due to trapped subdural and interhemispheric space air. It is observed as non-attenuating collections formed between the two frontal lobes and is specific to TPC [5,9]. The air bubble sign is the presence of multiple air bubbles scattered around the cisterns. It is caused mainly by a tear in the arachnoid membrane and is more common in TPC [5,9].

A simple pneumocephalus, even if it is massive, can be managed conservatively [10]. Conservative management involves the supine position, 100% supplemental oxygen, and frequent neurological monitoring to detect any signs/symptoms of increased ICP [7]. However, if the patient demonstrates any features of high ICP that indicate the development of TPC, an early neurosurgical referral, neurosurgical decompression, and repair of the causative defect are recommended [8]. Without timely intervention, TPC ultimately can lead to increased ICP, brain stem herniation, coma, and death [5].

In our case, the patient developed pneumocephalus by the
“inverted soda bottle effect” after drainage of CSF, and she clinically presented with acute seizures and a decrease in GCS, which indicated increased ICP. Thus, it was concluded that she did not have simple postoperative pneumocephalus but TPC. The reported incidence of pneumocephalus after the evacuation of CSF or blood from subdural space is 2.5% [8]. In our case, TPC was confirmed by a brain CT that showed the “Mount Fuji” sign, which is specific to TPC [5,9]. We managed this patient by keeping her in the supine position to prevent further CSF leaks, and she was given 100% supplemental oxygen to hasten the removal of intracranial nitrogen (air). Some authors, like Heidari [10] have reported successful conservative management over neurosurgical decompression in a patient with a massive pneumocephalus. Options of neurosurgical decompression include needle decompression either blind or under radiological guidance through an existing burr hole or craniotomy [1], controlled decompression via a closed water-seal drainage system [11], ventriculostomy for air in the ventricle [8], emergency decompression by creating new cranial Burr holes [8], and decompressive craniectomy [8]. Individual performance, outcome, or superiority of one procedure over those of another are not well studied in the reported medical literature, but there is a theoretical risk of intracranial infection with needle/drain decompression [12]. The choice of neurosurgical decompression technique depends on surgical expertise, institutional protocol, and availability of resources. In our patient, we managed TPC with left frontoparietal decompressive craniectomy, which resulted in seizure control and improvement of GCS.

Pneumocephalus can be prevented by using the following measures. (1) When using noninvasive respiratory support (high-flow nasal cannula or continuous positive pressure mask) in a patient with a history of head trauma, keep the flow rate or pressure as low as possible and closely monitor for any neurologic worsening or development of new neurological symptoms [6]. (2) When using invasive ventilation, avoid high airway pressure and hyperventilation [6]. (3) During anesthesia, avoid the use of nitrous oxide as an anesthetic agent in neurosurgical patients [7]. (4) During epidural injections, use saline instead of air to identify the epidural space [5]. (5) Most physicians recommend avoiding air travel for 2–8 weeks after surgery [13].

Although pneumocephalus and TPC are neurosurgical emergencies, their anesthetic and intensive care management have some important implications during their development and progress. Intensivists must maintain an in-depth knowledge of the etiopathogenesis of these conditions so that they can be diagnosed promptly, and the patient can be referred to a neurosurgeon for immediate surgical decompression. Thus, proper ICU and anesthetic management can prevent the development of pneumocephalus and its progress.

CONFLICT OF INTEREST

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

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ORCID

Bhushan Sudhakar Wankhade https://orcid.org/0000-0002-0288-129X
Maged Mohsen Kamel Beniamein https://orcid.org/0000-0001-7349-4724
Zeyad Faoor Alrais https://orcid.org/0000-0002-0249-2673
Jyoti Ittoop Mathew https://orcid.org/0000-0002-9970-6606
Ghaya Zeyad Alrais https://orcid.org/0000-0003-3076-3837

AUTHOR CONTRIBUTIONS

Conceptualization: BSW, MMKB. Data curation: BSW. Formal analysis: MMKB. Funding acquisition: ZFA. Methodology: BSW, MMKB, JIM. Project administration: ZFA. Visualization: MMKB, ZFA. Writing–original draft: BSW, GZA. Writing–review & editing: BSW, GZA, MMKB.

REFERENCES

In the article entitled “Methylprednisolone pulse therapy for critically ill patients with COVID-19: a cohort study,” some data of Table 3 was incorrectly presented. The correct Table 3 is as follows.

Table 3. Treatment and prognosis in critical or severe COVID-19 cases with control and pulse steroid groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control steroid (n=14)</th>
<th>Pulse steroid (n=30)</th>
<th>Total (n=44)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>High flow nasal cannula oxygen</td>
<td>14 (100)</td>
<td>29 (96.7)</td>
<td>43 (97.7)</td>
<td>0.490</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>4 (28.6)</td>
<td>6 (20.0)</td>
<td>10 (22.7)</td>
<td>0.527</td>
</tr>
<tr>
<td>Duration of mechanical ventilation (day)</td>
<td>18 (11–33)</td>
<td>8 (4–10)</td>
<td>10 (6–8)</td>
<td>0.063</td>
</tr>
<tr>
<td>Other treatment&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 (7.1)</td>
<td>3 (10.0)</td>
<td>4 (9.1)</td>
<td>0.759</td>
</tr>
<tr>
<td>Prone position&lt;sup&gt;b&lt;/sup&gt;</td>
<td>7 (50.0)</td>
<td>21 (70.0)</td>
<td>28 (63.6)</td>
<td>0.199</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>6 (42.9)</td>
<td>7 (23.3)</td>
<td>13 (29.5)</td>
<td>0.186</td>
</tr>
<tr>
<td>In-hospital mortality among moderate and mild ARDS groups</td>
<td>4 (44.4)</td>
<td>2 (13.3)</td>
<td>6 (25.0)</td>
<td>0.088</td>
</tr>
<tr>
<td>In-hospital mortality among severe ARDS group</td>
<td>2 (40.0)</td>
<td>5 (33.3)</td>
<td>7 (35.0)</td>
<td>0.933</td>
</tr>
<tr>
<td>28-Day mortality</td>
<td>5 (35.7)</td>
<td>7 (23.3)</td>
<td>12 (27.3)</td>
<td>0.390</td>
</tr>
<tr>
<td>Cause of death</td>
<td>0.255</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>4 (28.6)</td>
<td>5 (16.7)</td>
<td>9 (20.5)</td>
<td></td>
</tr>
<tr>
<td>Hepatic failure</td>
<td>2 (14.3)</td>
<td>0</td>
<td>2 (4.5)</td>
<td></td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>0</td>
<td>1 (3.3)</td>
<td>1 (2.3)</td>
<td></td>
</tr>
<tr>
<td>Renal failure</td>
<td>0</td>
<td>1 (3.3)</td>
<td>1 (2.3)</td>
<td></td>
</tr>
<tr>
<td>Length of hospital stay (day)</td>
<td>14 (12–24)</td>
<td>11 (9–16)</td>
<td>11 (8–17)</td>
<td>0.039&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Complication after steroid use</td>
<td>1 (7.1)</td>
<td>3 (9.9)</td>
<td>4 (9.0)</td>
<td>0.295</td>
</tr>
<tr>
<td>Uncontrolled hyperglycemia</td>
<td>0</td>
<td>2 (6.7)</td>
<td>2 (4.8)</td>
<td></td>
</tr>
<tr>
<td>Others&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1 (7.1)</td>
<td>1 (3.3)</td>
<td>2 (4.8)</td>
<td></td>
</tr>
</tbody>
</table>

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

<sup>a</sup> Other treatment includes renal replacement therapy or extracorporeal membrane oxygenation;
<sup>b</sup> Awake prone positioning;
<sup>c</sup> One gastrointestinal bleeding case in control steroid group and 1 candidemia case in pulse steroid group;
<sup>d</sup> Mann-Whitney U-test for comparisons between the control and pulse steroid groups.
Erratum to “Adjuvant intravenous immunoglobulin administration on postoperative critically ill patients with secondary peritonitis: a retrospective study”

Young Un Choi¹, Jun Gi Kim¹, Ji Young Jang², Tae Hwa Go³, Kwangmin Kim¹, Keum Seok Bae¹, Hongjin Shim¹

¹Department of Surgery, Yonsei University Wonju College of Medicine, Wonju, Korea
²Department of Surgery, National Health Insurance Service Ilsan Hospital, Goyang, Korea
³Department of Biostatistics, Yonsei University Wonju College of Medicine, Wonju, Korea

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In the article entitled “Adjuvant intravenous immunoglobulin administration on postoperative critically ill patients with secondary peritonitis: a retrospective study,” we would like to provide the missing funding information. We regret that the funding information was inadvertently omitted in the original publication. The correct funding statement should read as follows.

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Instructions for Authors

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

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

3) Units

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

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

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

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

2. Organization of Manuscript – Original Article

1) Title page

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

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

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

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

2) Abstract

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

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

Ex) Key Words: α2-adrenoceptor agonist; GABA; oxygen

3) Key Messages

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

4) Introduction

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

5) Materials and Methods

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

6) Results

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

7) Discussion

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

8) Conflict of Interest

If there are any conflicts of interest, authors should disclose them in the manuscript. Disclosures allow editors, reviewers, and readers to approach the manuscript with an understanding of the situation and background of the completed research. If there are no conflicts of interest, authors should include following sentence: “No potential conflict of interest relevant to this article was reported.”
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Funding for the research should be provided here. Providing a FundRef ID is suggested, including the name of the funding agency, the country, and if available, the number of the grant provided by the funding agency. If the funding agency does not have a FundRef ID, please ask the agency to contact the FundRef registry (e-mail: fundref.registry@crossref.org). A detailed description of the FundRef policy can be found at http://www.crossref.org/fundref/.

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

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

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

Examples of authors’ contributions are as follows:
Conceptualization: MHC. Data curation: JH. Formal analysis: YIA. Funding acquisition: MHC. Methodology: MHC, JH, YIA. Project administration: YIA. Visualization: MHC, JH, YIA. Writing – original draft: JH, YIA. Writing – review & editing: MHC, JH, YIA.

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

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

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

Examples of reference style
A. Journal Article
Authors. Article title. Journal title Published year;Volume: Start-End page.

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

D. Electronic Format
· Electronic publication before print
· Website

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

15) Figures and Illustrations
ACC publishes in full color and encourages authors to use color to increase the clarity of figures. Authors must submit figures and illustrations as electronic files. Images must be provided as TIFF files. JPEG is also acceptable when it is the original format. Each figure must be of good quality, higher than 300 dpi resolution with good contrast and sharpness. Figures must be sized to 4 inches. If possible, submit the original file without any modifications.
Submit files of figures and photographs separately from the text of the paper. Number figures as “Figure Arabic numeral” in the order of their citation (ex. Figure 1). If a figure is divided into more than two images, mark each figure with Arabic numerals and a capital letter (Ex. Figure 1A, Figure 1B). Authors should submit line drawings in black and white. Figures should be explained briefly in the titles. An individual should not be recognizable in photographs or X-ray films provided at the time of submission. Radiographic prints must have arrows for clarity if applicable. Pathological samples should be pictured with a measuring stick.

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

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. The main text should not exceed 1,000 words and the total number of references is limited to 5. Letters may be edited by the Editorial Board, and if necessary, responses from the author of the relevant paper may be provided. The responses should have the same format of Letters to Editor.

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.

2. Peer Review Process
1) Submitted manuscripts will be reviewed by 2 or more experts in the corresponding field. The Editorial Board may request authors to revise the manuscripts according to the reviewer’s opinion. After revising the manuscript, the author should upload the revised files with a reply to each item of the reviewer’s opinion. The revised part should be marked as red font with underline.
2) The author’s revisions should be completed within 30 days after the request. If it is not received by the due date, the Editorial Board will not consider it for publication again.
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.
5) The Editorial Board will make a final decision on the approval of the submitted manuscript for publication and can request any further corrections, revisions, and deletions of the article text if necessary. Statistical editing is also performed if the data requires professional statistical review by a statistician.

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

A. Confirmation by authors

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<th>Items</th>
<th>Check points</th>
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<td>Originality</td>
<td>☐ Confirm that neither the manuscript submitted nor any part of it has been published or is being considered for publication elsewhere.</td>
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<tr>
<td>Research ethics</td>
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<tr>
<td>Disclosure</td>
<td>☐ Disclose any commercial associations with specific products or financial support from any company.</td>
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<tr>
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<td>Thesis</td>
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<td>Presentation</td>
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<td>English proofreading</td>
<td>☐ State whether your article was revised or edited by a professional English proofreader.</td>
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B. Structure of article

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<td>Sequence</td>
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<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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<td>☐ Authors and affiliations: First, middle, and last names should be included for each author. If the author is affiliated with multiple departments, this should be included in a footnote by their name. If authors are affiliated with multiple departments and hospitals, affiliations should be arranged in the order of authors and demarcated with a number.</td>
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<td>☐ Running head: A running head of no more than 50 characters including letters and spaces should be included in English. If the included running head is inappropriate, the Editorial Board may revise it.</td>
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<td>☐ Corresponding author: The corresponding author’s name, postal code, address, telephone number, fax number, e-mail address should be included.</td>
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<td>☐ 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.</td>
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☐ Editorial  ☐ Original article  ☐ Review  ☐ Letter to the editor  ☐ Images in critical care

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(※ Please add the names and signatures of any additional authors)

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