

ORIGINAL RESEARCH

Risk factors associated with failed weaning from mechanical ventilation in septic patients admitted to an intensive care unit: a case-control study

Factores de riesgo de destete ventilatorio fallido en pacientes sépticos en una unidad de cuidado intensivo: estudio de casos y controles

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Abstract

Introduction: Several risk factors associated with weaning failure may be observed in septic patients requiring invasive mechanical ventilation.

Objective: To determine the risk factors associated with weaning failure in septic patients admitted to an intensive care unit (ICU) in Cali, Colombia, between January 2014 and June 2018.

Materials and methods: Case-control study conducted in 315 patients who required mechanical ventilation for more than 48 hours and were distributed as follows: 105 cases (weaning failure) and 210 controls (successful weaning). Information about sociodemographic and clinical variables was obtained from their medical records. A bivariate analysis was performed to determine the association between each independent variable and weaning failure. A multivariate analysis was also carried out using a logistic regression model in which the variables with a $p < 0.20$ in the bivariate analysis were entered. A significance level of $p \leq 0.05$ was considered.

Results: Requiring mechanical ventilation for more than 7 days (OR: 15.13; 95%CI: 8.25-27.74), having a high APACHE II score (mortality risk >50%) on ICU admission (OR: 3.16; 95%CI: 1.73-5.77), and having diuresis ≤ 0.5 mL/kg/h (OR: 1.87; 95%CI: 1.0-3.50) were significantly associated with weaning failure.

Conclusions: Requiring mechanical ventilation for more than 7 days, having diuresis ≤ 0.5 mL/kg/h, as well as a high APACHE II score on ICU admission were risk factors associated with failed weaning from mechanical ventilation in this study; however, age, blood urea nitrogen, creatinine, and positive fluid balance were not significantly associated with it, despite being described as risk factors in the literature.

Resumen

Introducción. En pacientes sépticos con requerimiento de ventilación mecánica invasiva pueden presentarse diferentes factores de riesgo de destete ventilatorio fallido.

Objetivo. Determinar los factores de riesgo de destete ventilatorio fallido en pacientes sépticos admitidos a una unidad de cuidados intensivos (UCI) de Cali, Colombia, entre enero de 2014 y junio 2018

Materiales y métodos. Estudio de casos y controles realizado en 315 pacientes que requirieron ventilación mecánica por más de 48 horas distribuidos así: 105 casos (destete fallido) y 210 controles (destete exitoso).

La información sobre variables sociodemográficas y clínicas se obtuvo a partir de la revisión de historias clínicas. Se realizó un análisis bivariado para determinar las asociaciones de cada variable independiente con el destete fallido y un análisis multivariado mediante un modelo de regresión logística en el que se ingresaron las variables que en el análisis bivariado tuvieron un valor $p < 0.20$. Se consideró un nivel de significancia de $p \leq 0.05$.

Resultados. Haber requerido ventilación mecánica por más de 7 días (OR: 15.13; IC95% 8.25-27.74), tener un puntaje APACHE II alto (riesgo de mortalidad >50%) al ingreso a UCI (OR: 3.16; 95%IC: 1.73-5.77) y tener diuresis ≤ 0.5 mL/kg/h (OR: 1.87; IC95% 1.0-3.50) se asociaron significativamente con el destete ventilatorio fallido.

Conclusiones. En el presente estudio, el requerimiento de ventilación mecánica mayor a 7 días, la diuresis ≤ 0.5 mL/kg/h y un puntaje APACHE II alto al ingreso a UCI fueron factores de riesgo para destete ventilatorio fallido, pero no se observó asociación con la edad, el nitrógeno ureico en sangre, la creatinina y el balance de líquidos positivos, a pesar de que estos han sido descritos como factores de riesgo en la literatura.

Introduction

Invasive mechanical ventilation (IMV) is one of the most important life support measures used in critically ill patients.¹ Once the cause that prompted its use is under control, immediate weaning should be considered; however, weaning failure occurs in approximately 10-20% of these patients.¹

Sepsis, a life-threatening organ dysfunction caused by dysregulated host response to infection, is a major global health concern and a common cause of admission and associated complications in intensive care units (ICUs).² Regarding prevalence, it has been estimated that more than 19 million cases occur every year and that the mortality rate in patients with sepsis is 30%, with an increase of up to 40% in older adults.²

Sepsis is characterized by relative and absolute hypovolemia caused by vasodilatation. In clinical terms, when sepsis occurs, heart rate and blood vessel constriction increase in order to maintain blood pressure and organ perfusion; however, when decompensation takes place, this clinical situation results in hypotension with hypoperfusion of peripheral organs, which leads to organ failure.³ During sepsis, any or several of the patient's organs may be affected, including the lungs, so treatment, in addition to broad-spectrum antibiotics, may involve the use of invasive mechanical ventilation, as well as aggressive fluid resuscitation.⁴

It has been reported that sepsis is associated with diaphragm muscle weakness in more than half of the patients on mechanical ventilation.⁵ In this regard, it has been described that in patients with sepsis, alterations are produced in the different steps of the muscular energy supply chain, including the abnormal distribution of blood flow (hypoxic ischemia) and its use (cytotoxic ischemia). Moreover, tumor necrosis factor-alpha (TNF- α) mediates the detrimental effects of cytokines on the contractile function of the diaphragm and ventilatory pump performance.⁶

Likewise, if excessive intravascular volume is administered during fluid resuscitation, regional alveolar interstitial edema may occur due to increased pulmonary capillary hydrostatic pressure. This increases the filtration of transvascular fluid into the interstitium and alveoli, while the capacity of lymphatic drainage markedly decreases, thus altering the diffusion of oxygen through the alveolar-capillary barrier.^{7,8}

Furthermore, it has been reported that in septic patients requiring ventilatory support, factors such as the nature of the disease that caused the sepsis, the presence of comorbidities, age, nutritional status, and/or the expertise of the interdisciplinary team in charge of their care can influence the prolongation of days on mechanical ventilation, regardless of the severity of organ dysfunction. These factors can thus have an impact on the increase in morbidity and mortality rates, as well as in the costs associated with the provision of healthcare to these patients.^{9,10}

For this reason, firstly, patients on mechanical ventilation should be evaluated daily to determine whether they will be able to breathe on their own, and secondly, risk factors associated with prolonged ventilatory support should be identified in order to take therapeutic measures tailored to the needs of each case. While several risk factors associated with weaning failure have been studied,¹¹ epidemiological data on specific risk factors in the context of physical therapy are limited and, therefore, establishing risk factors in the septic patient is a challenge.

Accordingly, the objective of the present study was to determine the risk factors associated with weaning failure in septic patients admitted to an ICU in Cali, Colombia, between January 2014 and June 2018.

Materials and methods

Study type and sample

Retrospective case-control study. In order to calculate sample size, and based on the available literature, the proportion of exposed controls was considered to be 20%, with a confidence level of 95%, a statistical power of 80%, an expected OR of 2.5, and a 2:1 case-control ratio.¹² On the basis of the foregoing and using the software available at www.openepi.com, a sample size of 315 patients (medical records) was calculated: 210 controls (septic patients with successful weaning) and 105 cases (septic patients with weaning failure).

Once the required number of cases and controls was established, the medical records that met the following inclusion criteria were reviewed: adult patients with a diagnosis of sepsis treated between January 2014 and June 2018 in the ICU of a quaternary healthcare center in Cali, Colombia, who required IMV for more than 48 hours and in whom the ventilatory weaning process was initiated. The diagnosis of sepsis was made by the specialized medical staff of the institution and according to inflammatory, hemodynamic and tissue perfusion parameters defined for this condition.

Groups were matched based on age, APACHE II (Acute Physiology And Chronic Health Evaluation II) score, days on mechanical ventilation, days in ICU, partial pressure of oxygen in arterial blood/fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) ratio, diuresis, 24-hour fluid balance, and cumulative fluid balance.

The medical records of patients undergoing tracheostomy on admission to the ICU, self-extubated patients, or those with upper airway alterations or diagnosed with neurological disease were not taken into account, since these types of conditions can affect the respiratory drive.¹³ Medical records with incomplete data on the variables of interest for the study were also excluded.

Definition of ventilator weaning and protocol

For the purposes of this study, ventilator weaning was defined as the discontinuation of IMV. Prior to its implementation, the medical and physical therapy professionals evaluated patients' tolerance to ventilator weaning by means of the spontaneous breathing trial (SBT), in which the patient was placed in continuous positive airway pressure (CPAP) mode at 6 cmH₂O plus pressure support ventilation (PSV) at 6 cmH₂O for >2 hours.¹⁰

Weaning failure was defined as the difficulty in tolerating an SBT or the need for reintubation within 72 hours after extubation, or up to 7 days after extubation if continued support with noninvasive mechanical ventilation was required. Extubation was defined as the process of removing the artificial airway in intubated patients.¹⁴

In addition, the following criteria were taken into account for the performance of the SBT: resolution of the acute phase of the disease that required the use of IMV, adequate oxygenation ($\text{PaO}_2 > 60 \text{ mmHg}$ with $\text{FiO}_2 < 0.4$ and positive end-expiratory pressure levels –PEEP– of 6 cmH₂O), $\text{PaO}_2/\text{FiO}_2 > 150$, hemodynamic stability in the absence of myocardial ischemia, heart rate <140 bpm, stable blood pressure (with or without vasoactive support), body temperature <38°C (no fever), non-significant respiratory acidosis with normal pH, hemoglobin >8 g/dL, Glasgow Coma Scale score >13, metabolic balance, adequate handling of secretions, and detectable inspiratory effort.

A patient was considered to tolerate SBT if the following conditions were met: arterial oxygen saturation (SpO₂) >90%, hemodynamic stability with heart rate <120 bpm and systolic blood pressure with changes <20% from baseline, and stable respiratory pattern with respiratory rate <30 rpm. Moreover, the following ventilation parameters were also taken into account to determine if the trial was tolerated: tidal volume >5 mL/kg ideal weight; respiratory frequency <15 L/min; and no evidence of agitation, anxiety, mental status deterioration, diaphoresis, cyanosis, dyspnea, increased respiratory effort, or cardiac arrhythmias.

Data collection

Weaning failure was considered as the dependent variable; independent variables included type of sepsis, presence of comorbidities, type of microorganism causing the infection, APACHE II score, days on mechanical ventilation, days of ICU stay, dialysis requirement, PaO₂/FiO₂, blood urea nitrogen (BUN) level, blood creatinine level, diuresis, 24-hour fluid balance, and cumulative fluid balance. Data on these variables, as well as sociodemographic data, were collected by reviewing the medical records.

Statistical analysis

A univariate analysis evaluating the behavior of the numerical variables was performed using the Shapiro–Wilk statistical test, assuming that the variable had a normal distribution with a significance value of $p \leq 0.05$ as the null hypothesis (H₀). Numerical variables with parametric distribution are described using means and standard deviations, while nonparametric variables are described by means of medians and interquartile ranges. Qualitative variables are expressed as absolute frequencies and percentages.

A bivariate analysis was also performed to determine the associations of each independent variable with the dependent variable using 2x2 tables, calculating the ORs for each variable and their corresponding 95% confidence intervals. For categorical variables, the chi-square test was used; in addition, when 25% of the cells had a value below 5, Fisher's exact test was employed. A significance level of $p \leq 0.05$ was considered.

Finally, a multivariate analysis was performed to determine the effect that each independent variable had on weaning failure by means of a logistic regression model, in which any possible confounding variables were adjusted. Thus, the model was constructed with the variables that in the bivariate analysis had a $p < 0.20$; then all these variables were evaluated one by one in the model and compared with each other using the likelihood ratio until a $p \leq 0.05$ was found, showing that the models were different. To determine the goodness of fit of the final model, the Hosmer–Lemeshow test was performed, using the null hypothesis that there was no difference between the observed values and the estimated values.

All statistical analyses were performed in the statistical software SPSS, version 22.

Ethical considerations

The study took into account the health research provisions established in Resolution 8430 of 1993 (article 11) of the Colombian Ministry of Health¹⁵ and the ethical principles for the conduct of biomedical research established in the Declaration of Helsinki.¹⁶ Moreover, the study was approved by the Institutional Ethics Committee of Clínica Amiga - Comfandi (Minutes CD-046509-S010010105) and by the Ethics Committee of the Universidad Libre – Cali Campus (Minutes 005-2019).

Results

The median age of the weaning failure group (cases) was 65 years, which was older than the control group (60 years); the majority of patients were male (55.24% in the case group and 62.86% in the control group). Sepsis of pulmonary origin was the most frequent type of sepsis in both groups (51.43% vs 48.09%, respectively). The most commonly found microorganisms in both groups were Gram-negative bacteria (42.86% vs. 45.24%, respectively). In addition, 90.79% of the participants had comorbidities, including chronic obstructive pulmonary disease, arterial hypertension, diabetes mellitus, and obesity.

The median number of days on mechanical ventilation was 13 days in cases and 5 days in controls. Overall, 75.23% of patients with weaning failure required more than 7 days of mechanical ventilation, while this situation occurred in only 17.14% of patients in the successful weaning group ($p=0.001$). No statistically significant differences were observed in the number of days of ICU stay between the two groups ($p=0.632$). The remainder of the general clinical and sociodemographic characteristics for each group are presented in Table 1.

Table 1. Overall clinical and sociodemographic characteristics of the participants.

| Variable | Weaning failure | | P value |
|-----------------------|-----------------|-----------------|---------|
| | Yes (cases) | No (controls) | |
| n (%) | 105 (33.33) | 210 (66.67) | |
| Age | | | |
| Median (IQR) | 67 (52 to 77) | 60.5 (47 to 72) | 0.031 |
| Range | (21 to 94) | (18 to 92) | |
| Sex | | | |
| n (%) | | | |
| Female | 47 (44.76) | 78 (37.14) | 0.193 |
| Male | 58 (55.24) | 132 (62.86) | |
| Site of sepsis | | | |
| n (%) | | | |
| Pulmonary | 54 (51.43) | 101 (48.09) | 0.314 |
| Abdominal | 18 (17.14) | 43 (20.48) | |
| Urinary | 21 (20.00) | 35 (16.67) | |
| Biliary tract | 0 | 7 (3.33) | |
| Soft tissues | 11 (10.48) | 18 (8.57) | |
| Gastrointestinal | 1 (0.96) | 6 (2.86) | |
| Comorbidities | | | |
| n (%) | | | |
| No | 6 (5.71) | 23 (10.95) | 0.13 |
| Yes | 99 (94.29) | 187 (89.04) | |
| Microorganism | | | |
| n (%) | | | |
| No bacteria | 10 (9.52) | 38 (18.09) | 0.126 |
| Gram Negative | 45 (42.86) | 95 (45.24) | |
| Gram Positive | 34 (32.38) | 55 (26.19) | |
| Fungi | 16 (15.24) | 22 (10.48) | |
| Dialysis | | | |
| n (%) | | | |
| No | 58 (55.24) | 155 (73.81) | 0.001 |
| Yes | 47 (44.76) | 55 (26.19) | |
| Days on IMV | | | |
| Median (IQR) | 13 (7.5 a 21) | 5 (4 a 7) | 0.000 |
| Range | (3 a 64) | (3 a 15) | |

IMV: invasive mechanical ventilation; IQR: interquartile range.

Source: Own elaboration.

Regarding bivariate analysis (Table 2), the following variables were dichotomized: age: ≤ 65 years and > 65 years; APACHE II score: $\leq 50\%$ and $> 50\%$ (mortality risk); days in ICU: ≤ 8 days and > 8 days; days on mechanical ventilation: ≤ 7 days and > 7 days; $\text{PaO}_2/\text{FiO}_2$: ≤ 200 and > 200 ; BUN: ≤ 20 mg/dL and > 20 mg/dL; creatinine level: ≤ 1.5 mg/dL and > 1.5 mg/dL; urine output: ≤ 0.5 mL/kg/h and > 0.5 mL/kg/h; 24-hour fluid balance: $\leq 1\text{L}$ and $> 1\text{L}$; and cumulative fluid balance: $\leq 3.4\text{L}$ and $> 3.4\text{L}$. This analysis found that the following potential risk factors were significantly associated with weaning failure: APACHE II score with a mortality risk $> 50\%$ (OR: 3.53, 95%CI: 2.1-5.95; $p=0.001$), mechanical ventilation > 7 days (OR: 14.68, 95%CI: 8-27.1; $p=0.001$), diuresis ≤ 0.5 mL/kg/h (OR: 3.85, 95%CI: 2-2.75; $p=0.001$), and accumulated fluid balance $> 3.4\text{L}$ (OR: 2.72, 95%CI: 1.5-5.1; $p=0.001$).

Table 2. Bivariate analysis. Association of the possible risk factors under consideration with weaning failure.

| Variable | OR (95%CI) | P value |
|---|----------------------|---------|
| APACHE II Score (risk of mortality) | | |
| $\leq 50\%$ | 1 | 0.001 |
| $> 50\%$ | 3.53 (2.10 to 5.95) | |
| Dialysis | | |
| Yes | 1 | 0.001 |
| No | 0.44 (0.73 to 1.27) | |
| Days in ICU | | |
| ≤ 8 days | 1 | 0.63 |
| > 8 days | 0.87 (0.48 to 1.59) | |
| Days on IMV | | |
| ≤ 7 days | 1 | 0.001 |
| > 7 days | 14.68 (8.0 to 27.10) | |
| $\text{PaO}_2/\text{FiO}_2$ | | |
| > 200 | 1 | 0.14 |
| ≤ 200 | 1.42 (0.85 to 2.38) | |
| BUN (mg/dL) | | |
| ≤ 20 | 1 | 0.27 |
| > 20 | 1.32 (0.77 to 2.26) | |
| Creatinine (mg/dL) | | |
| ≤ 1.5 | 1 | 0.61 |
| > 1.5 | 0.88 (0.51 to 1.48) | |
| Diuresis (ml/kg/h) | | |
| > 0.5 | 1 | 0.017 |
| ≤ 0.5 | 1.80 (1.07 to 3.02) | |
| 24h Balance (L) | | |
| ≤ 1 | 1 | 0.61 |
| > 1 | 1.13 (0.67 to 1.94) | |
| Accumulated fluid balance (L) | | |
| ≤ 3.4 | 1 | 0.001 |
| > 3.4 | 2.72 (1.50 a 5.10) | |

IMV: invasive mechanical ventilation; $\text{PaO}_2/\text{FiO}_2$: arterial pressure of oxygen in arterial blood/fraction of inspired oxygen; BUN: blood urea nitrogen; ICU: intensive care unit; OR: Odds Ratio; 95%CI: 95% confidence interval, $p < 0.05$. Source: Own elaboration.

Multivariate analysis

For logistic regression fitting, weaning failure was studied as an event and the following explanatory variables were included in the initial model: age: ≤ 65 years and > 65 years; APACHE II score: $\leq 50\%$ and $> 50\%$ (mortality risk); days on mechanical ventilation: ≤ 7 days and > 7 days; PaO₂/FiO₂: ≤ 200 and > 200 ; diuresis: ≤ 0.5 mL/kg/h and > 0.5 mL/kg/h; and accumulated fluid balance: ≤ 3.4 L and > 3.4 L.

Using logistic regression, it was found that being on mechanical ventilation for more than 7 days, having diuresis ≤ 0.5 mL/kg/h and having an APACHE II score $> 50\%$ increase the risk of weaning failure; these three variables were the only ones that were significantly associated in the logistic regression model. The results of the multivariate analysis are presented in Table 3.

Furthermore, when variables that did not support the prediction of the event were eliminated from the model by means of the manual selection method, i.e., one by one, it was found that the only variables that remained in the model were days on mechanical ventilation, APACHE II score, and diuresis. Thus, it was possible to establish that the requirement of mechanical ventilation for more than 7 days leads to a 15-fold increase in the probability of weaning failure (95%CI: 8.25-27.74), an APACHE score $> 50\%$ leads to a 3-fold increase in the probability of weaning failure (95%CI: 1.73-5.77), and diuresis ≤ 0.5 mL/kg/h leads to a 1.8-fold increase in the probability of weaning failure (95%CI: 1.0-3.50).

Table 3. Final logistic regression model.

| | Odds Ratio | 95%CI | P value |
|--|------------|---------------|---------|
| Age | | | |
| ≤ 65 years | 1 | | |
| > 65 years | 1.07 | 0.57 to 2.02 | 0.84 |
| Dialysis | | | |
| Yes | 1 | | |
| No | 0.80 | 0.35 to 1.83 | 0.59 |
| PaO₂/FiO₂ | | | |
| > 200 | 1 | | |
| ≤ 200 | 1.003 | 0.99 to 1.01 | 0.22 |
| Accumulated Balance L | | | |
| ≤ 3.4 | 1 | | |
| > 3.4 | 1.95 | 0.84 to 4.57 | 0.12 |
| APACHE II Score | | | |
| $\leq 50\%$ | 1 | | |
| $> 50\%$ | 3.16 | 1.73 to 5.77 | 0.001 |
| Days on IMV | | | |
| ≤ 7 days | 1 | | |
| > 7 days | 15.13 | 8.25 to 27.74 | 0.001 |
| Diuresis (ml/kg/h) | | | |
| > 0.5 | 1 | | |
| ≤ 0.5 | 1.87 | 1.00 to 3.50 | 0.05 |

IMV: invasive mechanical ventilation; PaO₂/FiO₂: arterial pressure of oxygen in arterial blood/fraction of inspired oxygen; OR: Odds Ratio; 95%CI: 95% confidence interval, $p < 0.05$.

Source: Own elaboration.

As mentioned in the materials and methods section, the Hosmer–Lemeshow test was used to evaluate the goodness-of-fit of the final model. The null hypothesis was that there was no difference between the observed values and the estimated values, obtaining a p value of 0.12, so the hypothesis was not rejected and, therefore, it was concluded that the proposed model was a good fit to the data.

Discussion

In the present study, conducted based on data obtained from the medical records of patients with a diagnosis of sepsis who required IMV for more than 48 hours, the following factors were associated with weaning failure: APACHE II score on admission to the ICU, presence of diuresis ≤ 0.5 mL/kg/h prior to weaning, and days on mechanical ventilation. In this sense, age, presence of comorbidities, state of consciousness, heart failure, cumulative fluid balance, PaO₂/FiO₂, APACHE II score, days on mechanical ventilation, and diuresis, among others, have been described as risk factors for weaning failure.¹⁷⁻²⁰

This study found that age was higher in cases than in controls ($p=0.031$); however, multivariate analysis did not show a statistically significant association between age and weaning failure (OR: 1.07; 95%CI: 0.57-2.02). In this regard, it is critical to highlight the importance of considering patient frailty, understood as a decrease in resistance and physiological reserves in the event of an illness and the subsequent increase in the risk of complications. In the case of septic patients, frailty has been reported to be associated with prolonged IMV (8 days in the frail group vs 5 days in the non-frail group; $p<0.01$),²¹ as well as with an increased risk of hospital readmission within 30 days after discharge (OR: 1.83; 95%CI: 1.38-2.34) and in-hospital mortality (OR: 1.81; 95%CI: 1.34-2.49).²² Bearing in mind that the older and frailer a septic patient is, the worse the outcome, nutritional support and early mobilization can be considered as comprehensive rehabilitation interventions in these patients in order to reduce the adverse effects of muscle weakness caused by a prolonged stay in the ICU due to sepsis and its complications.²³

In this study, a significant association was also observed between requiring IMV for more than 7 days and weaning failure (OR: 15.13; 95%CI: 8.25-27.74). This is consistent with the findings of the study by Ghiani *et al.*²⁴ in 263 tracheostomized patients on prolonged mechanical ventilation who were part of a prolonged weaning program in a respiratory care center in Germany, in which it was reported that the duration (in days) of mechanical ventilation on admission to the center and the duration of mechanical ventilation in the weaning center were significantly longer in patients with failed weaning ($n=137$) compared to those with successful weaning ($n=126$): 29 ± 24.8 vs. 24.2 ± 17.2 ; $p=0.034$ and 58.6 ± 32.1 vs. 45.2 ± 22.2 ; $p=0.001$, respectively. These findings are also similar to those reported by Upadya *et al.*²⁵ in a prospective study conducted in 87 mechanically ventilated patients admitted to an ICU, in which the median duration of mechanical ventilation was longer in patients with weaning failure ($n=48$) compared to those with successful weaning ($n=39$): median duration: 3 (1 to 14) days vs. 2 (1 to 8) days; $p=0.03$).

In this sense, although mechanical ventilation is used to counteract sepsis-induced ventilatory failure, it should also be considered that its prolongation has a negative impact on diaphragm function as a result of the positive regulation of proinflammatory cytokines and oxidative stress that it shares with sepsis. These synergistic events increase the risk of acquired weakness during ICU stay, which, in turn, will increase the patient's dependence on ventilatory support and, therefore, making weaning more difficult. To prevent this situation, one measure is to evaluate the daily goals to be achieved for the patient in terms of the Richmond Agitation and Sedation Scale (RASS), so that, on the one

hand, sedation can be titrated to reduce dependence on the ventilator and, on the other hand, whenever the clinical condition allows it, spontaneous modes of ventilation can be programmed progressively until successful weaning is achieved.^{26,27}

Furthermore, the present study also found that having an APACHE II score >50% (mortality risk) on admission to the ICU was significantly associated with weaning failure (OR: 3.16; 95%CI: 1.73-5.77). This finding is similar to that described by Chia-Cheng *et al.*²⁸ in a study of 163 adult patients with ventilator-associated pneumonia in which increased APACHE II scores behaved as an independent predictor of prolonged IMV (aOR: 1.35; aOR: 1.35; 95%CI: 1.04-1.74; $p=0.02$) with a sensitivity and specificity of 82% and 57%, respectively. In this sense, although it has been described that the APACHE II score can be used to predict the risk of mortality in the ICU,^{29,30} according to the results of the present study, it can be argued that it may be a useful tool to identify critically ill patients at risk of weaning failure.

Another factor that was associated with weaning failure in the present study was having diuresis ≤ 0.5 mL/kg/h (OR: 1.87; 95%CI: 1.0-3.5), which is consistent with the findings reported by Vieira *et al.*¹² in a study conducted in 140 oncology patients admitted to the ICU for different causes, including sepsis, who required IMV. In that study, it was found that the presence of oliguria, even transiently, increased the risk of prolonged ventilatory weaning (OR: 2.51; 95%CI: 1.24-5.08; $p=0.001$).

In this regard, various studies³¹⁻³⁴ agree that fluid resuscitation continues to be a challenge in the treatment of septic patients, since hemodynamic stability must be favored and the inadvertent presence of interstitial edema and its possible negative effects on the lungs must be avoided. Therefore, to facilitate weaning in these patients, it is necessary to establish the goals of fluid resuscitation based on strict hemodynamic and tissue perfusion monitoring, as well as to normalize fluid balance and maintain diuresis at normal levels through interventions such as the administration of diuretics and/or the use of dialysis.

Finally, it should be noted that this study has some limitations. First, the data come from a single ICU and the sample size is relatively small, so the findings reported here may not be fully representative for the country. Second, variables related to antibiotic resistance of the microorganism causing the infection that led to sepsis, use of vasodilator therapy and use of sedation, which are factors that could have been relevant in the statistical analysis, were not considered.

Conclusions

Requiring mechanical ventilation for more than 7 days, diuresis ≤ 0.5 mL/kg/h and a high APACHE II score upon admission to the ICU were risk factors for weaning failure in the present study. However, no association was observed with age, blood urea nitrogen, creatinine and positive fluid balance, although these aspects have been reported as risk factors in the literature.

A prospective study including relevant clinical variables associated with weaning, such as the use of vasoactive therapy and sedation, is recommended in order to obtain more data on all the factors that may affect successful weaning, undoubtedly contributing to improve the therapeutic interventions implemented in the care of these patients.

Conflicts of interest

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