J Bras Pneumol. 2023;49(4):e20230131
https://dx.doi.org/10.36416/1806-3756/e20230131

ORIGINAL ARTICLE

Predictors of prolonged ventilator weaning and mortality in critically ill patients with COVID-19

Marcella M Musumeci[1], Bruno Valle Pinheiro[2], Luciana Dias Chiavegato[1], Danielle Silva Almeida Phillip[1], Flavia R Machado[3], Fabrício Freires[3], Osvaldo Shigueomi Beppu[1], Jaquelina Sonoe Ota Arakaki[1], Roberta Pulcheri Ramos[1]

1. Disciplina de Pneumologia, Departamento de Medicina, Hospital São Paulo, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo (SP) Brasil.
2. Disciplina de Pneumologia, Universidade Federal de Juiz de Fora, Juiz de Fora (MG) Brasil.
3. Disciplina de Medicina Intensiva, Departamento de Anestesiologia, Dor e Medicina Intensiva, Hospital São Paulo, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo (SP) Brasil.

Submitted: 12 April 2023.
Accepted: 1 July 2023.

Study carried out in the respiratory and anesthesiology ICUs at the Hospital São Paulo, Universidade Federal de São Paulo, São Paulo (SP) Brasil.

ABSTRACT

Objective: To identify factors associated with prolonged weaning and mortality in critically ill COVID-19 patients admitted to ICUs and under invasive mechanical ventilation. **Methods:** Between March of 2020 and July of 2021, we retrospectively recorded clinical and ventilatory characteristics of critically ill COVID-19 patients from the day of intubation to the outcome. We classified the patients regarding the weaning period in accordance with established criteria. A logistic regression analysis was performed to identify variables associated with prolonged weaning and mortality. **Results:** The study involved 303 patients, 100 of whom (33.0%) had a prolonged weaning period. Most of the patients were male (69.6%), 136 (44.8%) had more than 50% of pulmonary involvement on chest CT, and 93 (30.6%) had severe ARDS. Within the prolonged weaning group, 62% died within 60 days. Multivariate analysis revealed that lung involvement greater than 50% on CT and delay from intubation to the first separation attempt from mechanical ventilation were significantly associated with prolonged weaning, whereas age and prolonged weaning were significantly associated with mortality. **Conclusions:** Prolonged weaning can be used as a milestone in predicting mortality in critically ill COVID-19 patients. Lung involvement greater than 50% on CT and delay from intubation to the first separation attempt from mechanical ventilation were identified as significant predictors of prolonged weaning. These results might provide valuable information for healthcare professionals when making clinical decisions regarding the management of critically ill COVID-19 patients who are on mechanical ventilation.

Keywords: COVID-19; Pneumonia, viral; Respiratory distress syndrome; Respiration, artificial; Ventilator weaning; Cohort studies; Hospital mortality; Patient outcome assessment.

INTRODUCTION

A SARS-CoV-2 infection can present with mild symptoms or progress to severe complications, including shock, multiple organ failure, arrhythmia, coagulopathy, cardiac injury, and ARDS.[1,2] According to cohorts in Italy and China, approximately 70% of patients with COVID-19 admitted to ICUs required ventilatory support, and most of them were mechanically ventilated for extended periods.[3,4] The severity of acute respiratory failure, the incidence of complications, and hospital structural limitations (such as shortages of ICU beds and of mechanical ventilators) have been cited as factors that could contribute to the longer duration of invasive mechanical ventilation (IMV) in COVID-19 patients.[5] It is worth noting that the longer the duration of mechanical ventilation is, the higher the morbidity and mortality rates in medical and surgical patients are.[6]

In addition to the aforementioned difficulties, challenges are added during the weaning phase, that is, the entire process of discontinuing IMV from the first effort to reduce ventilatory support to the removal of the endotracheal tube. This process is estimated to encompass about 40% of the total IMV time[7] and is therefore an important phase during the patient's stay in the ICU. The discontinuation of the mechanical ventilator depends on numerous factors and should be individualized and evaluated daily by a multidisciplinary team.[7-9]

Since mechanical ventilation is a critical phase during a patient's stay in the ICU, identifying factors that prolong weaning can allow for individualized approaches, such as transferring patients to facilities for extended weaning or recommending tracheostomy. Therefore, the objective of this study was to determine the factors associated with prolonged ventilator weaning and mortality in patients who were intubated due to acute respiratory failure caused by COVID-19.

Correspondence to:
Marcella M. Musumeci. Rua Martiniano de Carvalho, 669, apto. 806, Bela Vista, CEP 01321-001, São Paulo, SP, Brasil.
Tel.: 55 11 3385-4100 VoIP 1494. E-mail: marcella.marson@unifesp.br
Financial support: This study received financial support from the Brazilian *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (CAPES, Office for the Advancement of Higher Education; Funding Code 001).

METHODS

This retrospective cohort study was conducted in two ICUs dedicated to the care of subjects with COVID-19 in a large-size public teaching hospital in the city of São Paulo, Brazil, with a total of 75 ICU beds. The study was approved by the *Universidade Federal de São Paulo* Research Ethics Committee (Process no. CAAE 46961021.10000.5505). Since this is an observational study, informed consent was waived. Between March of 2020 and July of 2021, we included all subjects aged 18 years or older admitted to the participating ICUs who were mechanically ventilated due to confirmed COVID-19 pneumonia (clinical and tomographic findings suggestive of viral pneumonia and a positive RT-PCR test for SARS-CoV-2).

Because this is a retrospective study, the authors had no influence on either the choice of the optimal weaning moment or the way the process was conducted. The weaning process was performed based on literature criteria, clinical stability, and staff decision. A separation attempt (SA) from mechanical ventilation was considered a spontaneous breathing trial with pressure support less than or equal to 7 cmH_2O, followed by extubation or not, or an extubation performed without a previous spontaneous breathing trial. Successful weaning was defined as extubation without reintubation or death within the following 48 h,[9] regardless of the need for noninvasive ventilation (NIV) after extubation. For tracheostomized subjects, successful weaning was defined as spontaneous ventilation without any IMV support for 7 consecutive days.

Data were collected from the hospital's electronic medical record system by one of the researchers and kept confidential. The following variables were recorded on admission: age, sex, BMI, Simplified Acute Physiology Score 3 (SAPS 3),[10] Charlson Comorbidity Index (CCI),[11] endotracheal intubation (EI), severity of ARDS based on the Berlin definition,[12] and proportion of lung parenchyma affected by COVID-19 on chest CT as determined by a radiologist or the attending physician.

During the first 7 days of mechanical ventilation (or until extubation or death, whichever occurred first), we recorded the following ventilatory parameters: V_T, RR, F_{IO_2}, PEEP, plateau pressure (Pplat), driving pressure (ΔP, calculated as Pplat minus total PEEP), respiratory system compliance (C_{rs}, calculated as V_T divided by ΔP), and arterial blood gas analysis (including pH, Pao_2, $Paco_2$, and Pao_2/F_{IO_2}). Additionally, we collected information on the use of high-flow nasal cannula (HFNC) and NIV prior to EI.

The main outcome was to classify the subjects into four groups based on the weaning classification (known as the WIND study) by Béduneau et al.[9] These groups were as follows: "no weaning" group, consisting of subjects who had not undergone any SA from IMV; "short weaning" group, comprising subjects whose first SA resulted in either successful weaning or death within 1 day; "difficult weaning" group, consisting of subjects whose weaning was completed (either successfully or resulting in death) more than 1 day but less than one week after the first SA; and "prolonged weaning" group, comprising subjects in whom weaning was still not terminated 7 days after the first SA. For patients who failed and required reintubation in less than 48 h, the ventilatory period count was continuous.

The study also examined several secondary outcomes, including ventilator-associated pneumonia (VAP), pulmonary embolism (PE), reintubation rate, tracheostomy rate, number of ventilator-free days at day 28, ICU mortality, and 60-day mortality. Ventilator-free days were defined as the number of days during which the subjects were able to breathe spontaneously without any ventilatory assistance for 24 consecutive hours. If a subject died before day 28, they were considered to have had no ventilator-free days.

Statistical analysis

Data are presented as mean ± SD, median [IQR], or absolute and relative frequencies, as appropriate. For continuous variables with normal distribution, the groups were compared using one-way ANOVA; for categorical variables, groups were compared using the chi-square test. A multivariate logistic regression model was constructed to assess variables independently associated with prolonged weaning. The following variables were selected for initial assessment according to clinical relevance: age, sex, BMI, SAPS 3 at admission, CCI, pulmonary involvement on CT, previous HFNC or NIV use, arterial blood gas after EI (pH and Pao_2/F_{IO_2} ratio), ventilatory parameters after EI (ΔP; C_{rs}), and delay from EI to first SA. Variables with a $p < 0.20$ in the univariate logistic regression model were included in the multivariate model. Results were reported as OR (95% CI). A second multivariate logistic model was performed to assess if prolonged weaning was independently associated with ICU mortality. We built a directed acyclic graph (DAG) to choose the confounders and to avoid overfitting of the model.[13] Briefly, a DAG is a graphical tool that enables the visualization of the relationships between the exposure of interest, the outcome being studied, and all other variables that are associated in some way with at least two other variables in the diagram (supplementary figure).[14-16] The following confounders were selected for the DAG: age, SAPS 3, CCI, BMI, previous HFNC or NIV use, PE, VAP, worsening of ventilatory parameters (lower C_{rs}; higher ΔP) and of Pao_2/F_{IO_2} ratio within the first 7 days of IMV.

RESULTS

During the period studied, 817 subjects were admitted to the ICU, 303 of whom (37%) required IMV and were included in the study. After applying the WIND classification,[9] it was found that 102 subjects (33.7%) were classified in the "no weaning" group; 53 (17.5%), in the "short weaning" group; 48 (15.8%), in the "difficult weaning" group; and 100 (33.0%), in the

"prolonged weaning" group (Figure 1). Additional data on ventilatory and blood gas analysis variables at EI and the first SA day are presented in the supplementary material (supplementary table).

NIV or HFNC were used in 181 (59.7%) of the subjects before EI. At ICU admission, 136 (44.8%) of the subjects had more than 50% pulmonary involvement on chest CT, and 243 (80.1%) had a Pao_2/Fio_2 ratio < 150 mmHg on the first blood gas analysis after EI. Baseline characteristics of the subjects in each group are shown in Table 1. Almost half of the subjects (47.8%) had more than four comorbidities, the most prevalent ones being high blood pressure (in 64.1%), overweight (in 53.1%), diabetes mellitus (in 40.7%), and chronic kidney disease (in 33.5%). Significant differences were observed among the weaning groups for the following variables: age (p = 0.02); CCI (p = 0.04); severe ARDS (Pao_2/Fio_2 ratio < 150 mmHg; p < 0.01); pulmonary involvement over 50% on chest CT (p = 0.03); and previous use of NIV (p = 0.04). Tracheostomy was performed in 57 (18.8%) of the subjects, 47 (82%) of whom being in the prolonged weaning group, with a delay of 28 ± 10 days from EI.

Table 2 displays the outcomes of the study participants. The "prolonged weaning group had significantly higher VAP and tracheostomy rates than did the other groups (p < 0.01). Additionally, the 60-day mortality rate was significantly higher in this group (p < 0.01). Table 3 shows the variables that were independently associated with prolonged weaning. The proportion of lung involvement on chest CT (p = 0.04) and the delay from EI to first SA (p < 0.01) were found to be significant predictors of prolonged weaning. The study also found that the optimal cutoff point between EI and SA to indicate a risk for prolonged weaning was 9 days, with an AUC of 0.798 (95% CI, 0.734-0.862), a sensitivity of 72%, and a specificity of 79%. Table 4 displays the multivariate analyses that identified prolonged weaning and advanced age as independent risk factors for 60-day mortality (p < 0.01 for both).

DISCUSSION

In our study, we discovered two critical findings that shed light on the prolonged weaning process in critically ill patients with COVID-19. Firstly, we found that delaying the initiation of SA for more than 9 days after EI significantly increases the risk of prolonged weaning. Furthermore, our study uncovered an important association between prolonged weaning and mortality, emphasizing the need for close monitoring and timely interventions during the weaning process.

Our study revealed a noteworthy trend of patients dying before undergoing a weaning process, which aligns with the weaning profile identified in another study[17] that categorized the weaning of critically ill COVID-19 patients using the WIND study.[9] This finding is concerning and requires careful interpretation and investigation. There are several potential explanations for this trend. Firstly, the severity of the disease may contribute to a higher mortality rate before the opportunity for weaning arises.[18] Secondly, delayed recognition of weaning potential is another possibility, which could be attributed to various factors such as a focus on immediate life-saving interventions, the presence of comorbidities, or a lack of clear guidelines for identifying suitable weaning candidates.[19,20] Additionally, barriers to weaning, including unresolved underlying medical conditions, complications related to mechanical ventilation, or insufficient resources and expertise to effectively support the weaning process, may also play a role.[21] Identifying and addressing these

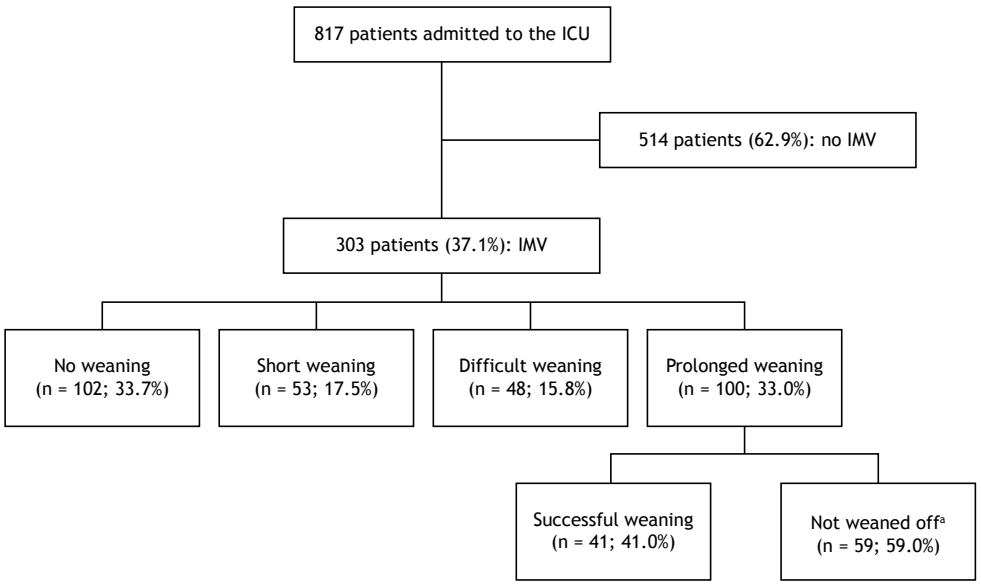

Figure 1. Flow chart of patient selection process and classification of selected patients in accordance with the classification system by Béduneau et al.[9] between March of 2020 and July of 2021. IMV: invasive mechanical ventilation. [a]After 60 days of follow-up.

Table 1. Demographic and clinical characteristics of critically ill COVID-19 patients on mechanical ventilation.[a]

Characteristic	All patients	Group				p*
		No weaning	Short weaning	Difficult weaning	Prolonged weaning	
	N = 303	n = 102 (33.7%)	n = 53 (17.5%)	n = 48 (15.8%)	n = 100 (33.0%)	
Age, years	61 ± 14	63 ± 14	55 ± 16	60 ± 14	61 ± 12	0.02
Gender, male	211 (69.6)	74 (72.5)	42 (79.2)	38 (79.1)	57 (57.0)	0.86
SAPS-3	58 ± 14	60 ± 15	55 ± 13	55 ± 15	58 ± 13	0.49
BMI, kg/m^2	28 ± 10	28 ± 6	27 ± 4	28 ± 4	28 ± 5	0.49
CCI > 4	145 (47.8)	49 (45.5)	6 (28.8)	16 (41.3)	74 (50.5)	0.04
Pao_2/Fio_2 < 150	243 (80.1)	87 (85.2)	35 (66.0)	33 (68.7)	88 (88.0)	< 0.01
CT lung involvement > 50%	136 (44.8)	47 (46.5)	7 (35.0)	12 (30.5)	70 (47.6)	0.03
EI before ICU admission	120 (39.6)	43 (42.1)	11 (20.7)	13 (27.0)	53 (53.0)	0.23
NIV before EI	134 (44.2)	37 (36.2)	9 (16.9)	21(43.7)	67 (67.0)	0.04
HFNC before EI	47(16.1)	11(10.8)	2 (3.7)	6 (12.5)	28 (28.0)	0.08
Delay from EI to first SA, days	6 [5-64]	-	6 [3-27]	17 [5-24]	23 [9-64]	< 0.01
Mechanical ventilation free days	3 [0-28]	-	19 [2-28]	10 [0-18]	2 [0-4]	0.06
Time on IMV, days	12 ± 9	11 ± 18	2 ± 1	6 ± 1	25 ± 15	< 0.01
Prone positioning	138 (45)	51 (50)	-	18 (37)	69 (69)	0.51
Neuromuscular blockade	224 (73)	79 (77)	3 (5)	32 (66)	100 (100)	0.67
Length of ICU stay, days	19 [11-173]	10 [5-172]	13 [10-56]	20 [14-79]	37 [26-128]	< 0.01
Survivors, length of ICU stay, days	19 [12-106]	-	13 [10-47]	22 [14-58]	53 [29-128]	< 0.01

SAPS-3: Simplified Acute Physiology Score 3; CCI: Charlson Comorbidity Index; EI: endotracheal intubation; NIV: noninvasive ventilation; HFNC: high-flow nasal cannula; SA: separation attempt; IMV: invasive mechanical ventilation. [a]Values are expressed as n (%), mean ± SD, or median [IQR]. *p-value states an overall comparison between the groups.

Table 2. Outcomes of critically ill COVID-19 patients on mechanical ventilation.[a]

Outcome	Group				p*
	No weaning	Short weaning	Difficult weaning	Prolonged weaning	
	n = 102 (33.7%)	n = 53 (17.5%)	n = 48 (15.8%)	n = 100 (33.0%)	
Reintubation	-	5 (9.4)	9 (18.7)	26 (26.0)	0.05
Tracheostomy	6 (5.8)	0 (0)	4 (8.3)	47 (47.0)	< 0.01
Pulmonary embolism	15 (14.8)	3 (5.6)	8 (16.6)	25 (25.0)	0.47
VAP	29 (28.7)	6 (11.3)	14 (29.1)	69 (69.0)	< 0.01
60-day mortality	102 (100)	3(5.6)	9 (18.7)	62 (62.0)	< 0.01

VAP: ventilator-associated pneumonia. [a]Values are expressed as n (%). *p-value states an overall comparison between the groups.

barriers is crucial for enhancing patient management and optimizing outcomes.

We observed that approximately one-third of the patients in our study experienced a prolonged weaning process. In our cohort, the mean duration of IMV was 12 days, slightly longer than the median duration of 8 days reported in an international COVID-19 cohort study.[21] This extended duration of IMV may contribute to the heightened risk of prolonged weaning observed in our study. However, a critical finding emerged from our analysis, revealing a significant association between delayed SA and extended duration of weaning. This association suggests that early initiation of SA plays a crucial role in facilitating a smoother and more efficient weaning process. When SA is delayed, patients may remain in a deeper sedation state[19] for a prolonged period, resulting in muscle weakness,[22] deconditioning, and increased challenges in liberating these patients from IMV. The implications of our findings align with the results of a meta-analysis on liberation from IMV, emphasizing the substantial challenges encountered in this process.[23] That meta-analysis indicated that only 50% of patients who required IMV for more than 17 days were successfully liberated, highlighting the complexity of prolonged weaning in critically ill patients, including those with COVID-19. Indeed, a study[24] that compared the weaning process between patients with COVID-19-associated ARDS and those with non-COVID-19 ARDS revealed that COVID-19 patients had a longer duration of IMV and encountered more challenges during the weaning transition, primarily due to weaning unreadiness. The presence of uncontrolled immune responses in COVID-19 patients may hinder lung recovery and complicate the assessment of readiness for ventilatory weaning.[20,25]

The association between pulmonary involvement on chest CT and prolonged weaning also raises significant concerns. Chest CT has been widely used during the

Table 3. Binary univariate logistic regression analysis of factors associated with prolonged weaning in critically ill COVID-19 patients on mechanical ventilation.

Variable	OR (95% CI)	p	OR (95% CI)	p
Age, years	1.104 (0.993-1.035)	0.17	1.027 (0.994-1.061)	0.13
Gender, male	1.145 (0.625-2.099)	0.66		
BMI, kg/m^2	1.027 (0.996-1.093)	0.39		
CCI	1.418 (0.987-2.036)	0.59		
SAPS-3	1.029 (0.994-1.065)	0.11	0.988 (0.990-1.006)	0.37
CT lung involvement > 50%	2.007 (1.347-2.990)	<0.01	1.765 (1.015-3.070)	0.04
NIV or HFNC before EI	0.886 (0.505-1.555)	0.67		
pH[a]	0.999 (0.992-1.006)	0.27		
Pao_2/Fio_2[a]	0.989 (0.984-0.995)	< 0.01	1.020 (0.710-1.465)	0.91
C_{rs}[a]	0.973 (0.935-1.014)	0.19	0.978 (0.936-1.022)	0.32
ΔP[a]	0.956 (0.835-1.003)	0.50		
Delay from EI to first SA	1.195 (1.125-1.269)	< 0.01	1.249 (1.131-1.380)	< 0.01

CCI: Charlson Comorbidity Index; SAPS-3: Simplified Acute Physiologic Score 3; NIV: noninvasive ventilation; HFNC: high-flow nasal cannula; EI: endotracheal intubation; C_{rs}: respiratory system compliance; ΔP: driving pressure; and SA: separation attempt. [a]First values after EI.

Table 4. Binary logistic regression analysis of factors associated with mortality in critically ill COVID-19 patients on mechanical ventilation.[a]

Variable	Multivariate analysis	
	OR (95% CI)	p
Age	1.077 (1.039-1.116)	< 0.01
BMI	0.972 (0.913-1.035)	0.37
CCI	0.712 (0.434-1.167)	0.17
SAPS 3	1.006 (0.975-1.039)	0.64
CT lung involvement (>50%)	1.211 (0.842-1.744)	0.30
NIV or HFNC before EI	0.983 (0.460-2.098)	0.96
Pulmonary embolism	1.534 (0.696-3.384)	0.28
VAP	1.118 (0.527-2.369)	0.77
Pao_2/Fio_2[b]	1.003(0.994-1.012)	0.52
C_{rs}[b]	1.011(0.948-1.078)	0.74
ΔP[b]	0.966 (0.879-1.061)	0.46
Prolonged weaning	6.579 (2.649-11.441)	< 0.01

CCI: Charlson Comorbidity Index; SAPS-3: Simplified Acute Physiologic Score 3; NIV: noninvasive ventilation; HFNC: high-flow nasal cannula; EI: endotracheal intubation; VAP: ventilator-associated pneumonia; C_{rs}: respiratory system compliance; and ΔP: driving pressure. [a]The entire sample is included except for the no weaning group. [b]It represents the worst value within the first 7 days on invasive mechanical ventilation.

pandemic to assess the severity of COVID-19, identify complications, and predict disease progression in severe cases.[26] Greater pulmonary involvement, as observed on chest CT, directly impacts on pulmonary function and dyspnea scores.[27] Consistently with our cohort, Maes et al.[27] found that patients with more severe involvement on chest CT images tended to be older and had a higher incidence of comorbidities. Understanding this association has important clinical implications. It highlights the importance of considering the extent of lung involvement identified on chest CT when evaluating patients' readiness for weaning and planning appropriate management strategies. Future research should focus on investigating the specific characteristics of lung involvement on chest CT that are associated with prolonged weaning. This might help refine risk stratification and guide decisions regarding the timing and intensity of interventions during the weaning process.

Finally, our study revealed that prolonged weaning patients have a higher incidence of complications, mainly VAP. Although the association between VAP and mortality in COVID-19 is well known,[27,28] our study did not directly indicate a significant impact of VAP on mortality outcomes. However, it is important to acknowledge that VAP can lead to complications and prolong recovery, potentially contributing to delayed weaning.[28]

In contrast, our findings identified prolonged weaning as an independent factor associated with poor prognosis, influenced by a complex interplay of multiple factors affecting patient outcomes. Firstly, underlying disease severity can compromise lung function and reduce physiological reserves, making the weaning process more challenging and increasing the risk of adverse outcomes, including mortality.[29] Secondly, prolonged mechanical ventilation and immobility during critical

illness can result in muscle wasting and weakness, which can impact outcomes.[23,24] Additionally, inflammatory responses, especially in severe cases of COVID-19, can cause lung damage and hinder lung function recovery.[20,30] Persistent inflammation and unresolved pulmonary complications may delay the weaning process and contribute to an increased risk of mortality.[30]

These factors highlight the complexity of the relationship between prolonged weaning and mortality. The duration of weaning alone does not fully explain the observed outcomes. It is crucial to consider underlying disease severity, muscle weakness, and inflammation as intertwined factors that influence the impact of prolonged weaning on mortality. By understanding and addressing these factors, healthcare professionals can develop targeted interventions and optimize the management of patients undergoing the weaning process, ultimately improving patient outcomes.

Our study has several methodological limitations that should be acknowledged. Firstly, it is retrospective in nature, which may introduce biases in data collection and analysis. Secondly, the study was conducted in a single-center public service with challenges related to limited supplies and staff, potentially affecting the generalizability of the findings. Additionally, important data on the use of sedatives and incidence of delirium were not collected, which could provide further insights into the factors influencing the outcomes. Moreover, the absence of a comparison group of non-COVID-19 patients with respiratory failure limits our ability to make direct comparisons and draw conclusive interpretations. Despite all these limitations, it is important to consider that our research was carried out during the early waves of the COVID-19 pandemic in Brazil, when vaccination coverage was low and there was a presence of highly virulent SARS-CoV-2 variants. Therefore, caution should be exercised when generalizing these findings to the current context, because the dynamics of the pandemic and the availability of preventive measures and treatments may have evolved.

In conclusion, prolonged weaning is a valuable indicator for predicting mortality in critically ill COVID-19 patients. Our study identified two significant factors associated with prolonged weaning: lung involvement greater than 50% on chest CT and delay in performing the first SA after EI. Addressing the prolonged duration of mechanical ventilation and optimizing the timing of SA are crucial steps towards improving the weaning process and ultimately enhancing patient outcomes. Future research should focus on developing strategies that promote early awakening, minimize sedation duration, and streamline the weaning process for critically ill patients with COVID-19.

AUTHOR CONTRIBUTIONS

MMM, BVP, and OSB: study design. MMM and FF: data collection. MMM, BVP, and RPR: statistical analysis. MMM, RPR, LDC, and DSAP: drafting of the manuscript. RPR, JSOA, and FRM: critical review of the manuscript. All of the authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Hu B, Guo H, Zhou P, Shi ZL. Characteristics of SARS-CoV-2 and COVID-19 [published correction appears in Nat Rev Microbiol. 2022 May;20(5):315]. Nat Rev Microbiol. 2021;19(3):141-154. https://doi.org/10.1038/s41579-020-00459-7
2. Li X, Ma X. Acute respiratory failure in COVID-19: is it "typical" ARDS?. Crit Care. 2020;24(1):198. https://doi.org/10.1186/s13054-020-02911-9
3. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China [published correction appears in JAMA. 2021 Mar 16;325(11):1113]. JAMA. 2020;323(11):1061-1069. https://doi.org/10.1001/jama.2020.1585
4. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy [published correction appears in JAMA. 2021 May 25;325(20):2120]. JAMA. 2020;323(16):1574-1581. https://doi.org/10.1001/jama.2020.5394
5. COVID-ICU Group on behalf of the REVA Network and the COVID-ICU Investigators. Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: a prospective cohort study. Intensive Care Med. 2021;47(1):60-73. https://doi.org/10.1007/s00134-020-06294-x
6. Hur K, Price CPE, Gray EL, Gulati RK, Maksimoski M, Racette SD, et al. Associated With Intubation and Prolonged Intubation in Hospitalized Patients With COVID-19 [published correction appears in Otolaryngol Head Neck Surg. 2020 Jul;163(1):NP1]. Otolaryngol Head Neck Surg. 2020;163(1):170-178. https://doi.org/10.1177/0194599820929640
7. Geiseler J, Westhoff M. Weaning from invasive mechanical ventilation [Article in German]. Med Klin Intensivmed Notfmed. 2021;116(8):715-726. https://doi.org/10.1007/s00063-021-00858-5
8. Peñuelas O, Frutos-Vivar F, Fernández C, Anzueto A, Epstein SK, Apezteguía C, et al. Characteristics and outcomes of ventilated patients according to time to liberation from mechanical ventilation. Am J Respir Crit Care Med. 2011;184(4):430-437. https://doi.org/10.1164/rccm.201011-1887OC
9. Béduneau G, Pham T, Schortgen F, Piquilloud L, Zogheib E, Jonas M, et al. Epidemiology of Weaning Outcome according to a New Definition. The WIND Study. Am J Respir Crit Care Med. 2017;195(6):772-783. https://doi.org/10.1164/rccm.201602-0320OC
10. Capuzzo M, Scaramuzza A, Vaccarini B, Gilli G, Zannoli S, Farabegoli L, et al. Validation of SAPS 3 Admission Score and comparison with SAPS II. Acta Anaesthesiol Scand. 2009;53(5):589-594. https://doi.org/10.1111/j.1399-6576.2009.01929.x
11. Brusselaers N, Lagergren J. The Charlson Comorbidity Index in Registry-based Research. Methods Inf Med. 2017;56(5):401-406. https://doi.org/10.3414/ME17-01-0051
12. ARDS Definition Task Force; Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012;307(23):2526-2533. https://doi.org/10.1001/jama.2012.5669
13. VanderWeele TJ, Robins JM. Four types of effect modification: a classification based on directed acyclic graphs. Epidemiology. 2007;18(5):561-568. https://doi.org/10.1097/EDE.0b013e318127181b
14. Textor J, van der Zander B, Gilthorpe MS, Liskiewicz M, Ellison GT. Robust causal inference using directed acyclic graphs: the R package 'dagitty'. Int J Epidemiol. 2016;45(6):1887-1894. https://doi.

org/10.1093/ije/dyw341

15. Suttorp MM, Siegerink B, Jager KJ, Zoccali C, Dekker FW. Graphical presentation of confounding in directed acyclic graphs. Nephrol Dial Transplant. 2015;30(9):1418-1423. https://doi.org/10.1093/ndt/gfu325
16. Staplin N, Herrington WG, Judge PK, Reith CA, Haynes R, Landray MJ, et al. Use of Causal Diagrams to Inform the Design and Interpretation of Observational Studies: An Example from the Study of Heart and Renal Protection (SHARP). Clin J Am Soc Nephrol. 2017;12(3):546-552. https://doi.org/10.2215/CJN.02430316
17. Dorado JH, Navarro E, Plotnikow GA, Gogniat E, Accoce M; EpVAr Study Group. Epidemiology of Weaning From Invasive Mechanical Ventilation in Subjects With COVID-19. Respir Care. 2023;68(1):101-109. https://doi.org/10.4187/respcare.09925
18. Domecq JP, Lal A, Sheldrick CR, Kumar VK, Boman K, Bolesta S, et al. Outcomes of Patients With Coronavirus Disease 2019 Receiving Organ Support Therapies: The International Viral Infection and Respiratory Illness Universal Study Registry [published correction appears in Crit Care Med. 2021 May 1;49(5):e562]. Crit Care Med. 2021;49(3):437-448. https://doi.org/10.1097/CCM.0000000000004879
19. Han WH, Lee JH, Chun JY, Choi YJ, Kim Y, Han M, et al. Predicting factors associated with prolonged intensive care unit stay of patients with COVID-19. Acute Crit Care. 2023;38(1):41-48. https://doi.org/10.4266/acc.2022.01235
20. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries [published correction appears in JAMA. 2016 Jul 19;316(3):350] [published correction appears in JAMA. 2016 Jul 19;316(3):350]. JAMA. 2016;315(8):788-800. https://doi.org/10.1001/jama.2016.0291
21. Pham T, Heunks L, Bellani G, Madotto F, Aragao I, Beduneau G, et al. Weaning from mechanical ventilation in intensive care units across 50 countries (WEAN SAFE): a multicentre, prospective, observational cohort study [published correction appears in Lancet Respir Med. 2023 Mar;11(3):e25]. Lancet Respir Med. 2023;11(5):465-476. https://doi.org/10.1016/S2213-2600(22)00449-0
22. Boussuges A, Habert P, Chaumet G, Rouibah R, Delorme L, Menard A, et al. Diaphragm dysfunction after severe COVID-19: An ultrasound study. Front Med (Lausanne). 2022;9:949281. https://doi.org/10.3389/fmed.2022.949281
23. Damuth E, Mitchell JA, Bartock JL, Roberts BW, Trzeciak S. Long-term survival of critically ill patients treated with prolonged mechanical ventilation: a systematic review and meta-analysis. Lancet Respir Med. 2015 Jul;3(7):544-553. https://doi.org/10.1016/S2213-2600(15)00150-2
24. Melamed R, Paz F, Jepsen S, Smith C, Saavedra R, Mulder M, et al. Prognostic factors and outcomes in COVID-19 patients requiring prolonged mechanical ventilation: a retrospective cohort study. Ther Adv Respir Dis. 2022;16:17534666221086415. https://doi.org/10.1177/17534666221086415
25. Gendreau S, Benelli B, Delière M, Tuffet S, de Prost N, Razazi K, et al. Partitioning Mechanical Ventilator Duration in COVID-19-related Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med. 2022;206(1):114-118. https://doi.org/10.1164/rccm.202108-1963LE
26. Li K, Wu J, Wu F, Guo D, Chen L, Fang Z, et al. The Clinical and Chest CT Features Associated With Severe and Critical COVID-19 Pneumonia. Invest Radiol. 2020;55(6):327-331. https://doi.org/10.1097/RLI.0000000000000672
27. Maes M, Higginson E, Pereira-Dias J, Curran MD, Parmar S, Khokhar F, et al. Ventilator-associated pneumonia in critically ill patients with COVID-19 [published correction appears in Crit Care. 2021 Apr 6;25(1):130]. Crit Care. 2021;25(1):25. https://doi.org/10.1186/s13054-021-03460-5
28. Ippolito M, Misseri G, Catalisano G, Marino C, Ingoglia G, Alessi M, et al. Ventilator-Associated Pneumonia in Patients with COVID-19: A Systematic Review and Meta-Analysis. Antibiotics (Basel). 2021;10(5):545. https://doi.org/10.3390/antibiotics10050545
29. Reddy MP, Subramaniam A, Chua C, Ling RR, Anstey C, Ramanathan K, et al. Respiratory system mechanics, gas exchange, and outcomes in mechanically ventilated patients with COVID-19-related acute respiratory distress syndrome: a systematic review and meta-analysis. Lancet Respir Med. 2022;10(12):1178-1188. https://doi.org/10.1016/S2213-2600(22)00393-9
30. Bordon J, Akca O, Furmanek S, Cavallazzi RS, Suliman S, Aboelnasr A, et al. Acute Respiratory Distress Syndrome and Time to Weaning Off the Invasive Mechanical Ventilator among Patients with COVID-19 Pneumonia. J Clin Med. 2021;10(13):2935. https://doi.org/10.3390/jcm10132935