Epidemiology of Weaning From Invasive Mechanical Ventilation in Subjects With COVID-19

Javier H Dorado, Emiliano Navarro, Gustavo A Plotnikow, Emiliano Gogniat, and Matías Accoce; on behalf of the EpVAr Study Group

BACKGROUND: Patients requiring mechanical ventilation due to COVID-19 have different characteristics of evolution and outcome compared to the general ICU population. Although early weaning from mechanical ventilation is associated with improved outcomes, inadequate identification of patients unable to be weaned may lead to extubation failure and increased days on mechanical ventilation. Outcomes related to mechanical ventilation weaning in this population are scare and inconclusive. Therefore, the objective of this study was to describe the characteristics of mechanical ventilation weaning in subjects with acute respiratory failure induced by COVID-19. METHODS: This was a multi-center, prospective cohort study. We included adult subjects requiring at least 12 h of mechanical ventilation due to COVID-19 infection admitted to any participating ICUs. Characteristics of the mechanical ventilation weaning and extubation process, as well as clinical results, were the primary outcome variables. Weaning types were defined according to previously described and internationally recognized categories. RESULTS: Three hundred twenty-six subjects from 8 ICUs were included. A spontaneous breathing trial (SBT) was not performed in 52.1% of subjects. One hundred twenty-eight subjects were extubated, and 29.7% required re-intubation. All the subjects included could be classified by Weaning according to a New Definition (WIND) classification (group 0 = 52.1%, group 1 = 28.5%, group 2 = 8.0%, and group 3 = 11.3%) with statistically significant differences in duration of mechanical ventilation ($P < .001$) and ICU length of stay ($P < .001$) between groups. CONCLUSIONS: The mechanical ventilation weaning process in subjects with COVID-19 was negatively affected by the disease, with many subjects never completing an SBT. Even though temporal variables were modified, the clinical outcomes in each weaning group were similar to those previously reported. *Key words: mechanical ventilation; ICU; epidemiology; weaning mechanical ventilation; respiratory distress syndrome; COVID-19.* [Respir Care 2023;68(1):101–109. © 2023 Daedalus Enterprises]

Introduction

Mechanical ventilation is a life-sustaining strategy frequently implemented in the ICU.[1] During the COVID-19 pandemic, millions of patients have caused an unprecedented breakdown in health care systems worldwide, resulting in increased hospital admissions, demand for ICU beds, and the need for health care professionals.[2]

Epidemiological studies have shown that the patients that require mechanical ventilation due to acute respiratory failure induced by COVID-19 have a different evolution and outcomes compared with a general ICU population.[3-8] In Argentina, 2 recent multi-center epidemiological studies on mechanical ventilation highlighted marked differences between subjects with and without COVID-19. In these studies, the main differences were a greater need for adjuvant therapies for refractory hypoxemia, a longer stay in the ICU, and a significantly longer duration of mechanical ventilation in the SATICOVID study.[3,9] Unfortunately, studies describing the ventilatory weaning process in this population are scarce and results are inconclusive.

Approximately half of the time on mechanical ventilation is spent in the weaning process.[10] Although early weaning is associated with better outcomes, inadequate identification of patients unable to be weaned may lead to a higher number of extubation failures and days on mechanical ventilation, both of which are associated with increased mortality.[11] The protocolized use of spontaneous awakening trials (SATs) combined with an appropriate spontaneous breathing trial (SBT) has been shown to reduce

days on mechanical ventilation.[12-17] During the pandemic, recommendations have been made on minimizing bedside time and ventilatory circuit disconnections to minimize the risk of exposure of health care staff.[18,19] Consequently, adherence to the ABCDEF bundle has been extremely low. These particular situations may jeopardize the weaning process with consequent increased ICU morbidity and mortality.[20] Few studies have provided data on the mechanical ventilation weaning and extubation process in subjects with COVID-19, and it is known that failure of weaning and extubation is associated with poor outcomes.[21]

Therefore, the main objective of this study was to describe the characteristics of weaning from mechanical ventilation in subjects with COVID-19 and outcomes according to the different weaning categories.[10,11]

QUICK LOOK

Current knowledge

Mechanically ventilated patients with COVID-19 have different features regarding evolution and outcomes. In this population, the duration of mechanical ventilation and re-intubation rate are high.

Take-Home Message of the Study

Most subjects with COVID-19 did not initiate the process of weaning from mechanical ventilation. At the end of the ICU stay, only 4 of 10 subjects were successfully weaned. Despite increased duration of mechanical ventilation in all the weaning groups, the results in terms of mortality were similar to what has already been reported.

Methods

Study Design and Inclusion Criteria

We conducted a multi-center, prospective cohort study following STROBE recommendations.[22] The original study protocol was approved by the Argentinian Critical Care Society Ethics Committee with number N°1516 (approval date: March 10, 2020) and was retrospectively registered on ClinicalTrials.gov (number NCT05049200). Each participating health care center obtained the corresponding approval from its own ethics committee.

We consecutively recruited all patients > 18 y who required invasive mechanical ventilation for at least 12 h for acute respiratory failure due to COVID-19 (positive polymerase chain reaction test) between April 1–August 30, 2020. Exclusion criteria were patients admitted to pediatric ICU and surgery recovery rooms. In the case of readmission of subjects already enrolled requiring a new cycle of mechanical ventilation, only the first cycle was considered for the analysis. Elimination criteria were applied in subjects with > 10.0% missing data in clinically relevant variables.

A retrospective post hoc data collection was performed including subjects who required mechanical ventilation for acute respiratory failure of etiology other than COVID-19. The aim of this analysis was to have a parameter in a reference sample to make a descriptive comparison of the probable effect of COVID-19 on mechanical ventilation weaning variables.

Procedure

Relevant data were collected between 8–11 AM by the principal investigator of each participating center or by a person

Mr Dorado is affiliated with Capítulo de Kinesiología Intensivista, Sociedad Argentina de Terapia Intensiva, CABA, Argentina; and Sanatorio Anchorena San Martin, Provincia de Buenos Aires, Argentina. Mr Navarro is affiliated with Capítulo de Kinesiología Intensivista, Sociedad Argentina de Terapia Intensiva, CABA, Argentina; and Centro del Parque, CABA, Argentina. Mr Plotnikow is affiliated with Capítulo de Kinesiología Intensivista, Sociedad Argentina de Terapia Intensiva, CABA, Argentina; Universidad Abierta Interamericana, Facultad de Medicina y Ciencias de la Salud, CABA, Argentina; Hospital Británico de Buenos Aires, CABA, Argentina; and Director del Grupo de Estudios Especializados en VM, Universidad Abierta Interamericana, CABA, Argentina. Mr Gogniat is affiliated with Capítulo de Kinesiología Intensivista, Sociedad Argentina de Terapia Intensiva, CABA, Argentina. Mr Accoce is affiliated with Capítulo de Kinesiología Intensivista, Sociedad Argentina de Terapia Intensiva, CABA, Argentina; Sanatorio Anchorena San Martin, Provincia de Buenos Aires, Argentina; and Universidad Abierta Interamericana. Facultad de Medicina y Ciencias de la Salud, CABA, Argentina.

EpVAr Study Group: Norberto Tiribelli (Complejo Médico PFA Churruca Visca, CABA, Argentina), Roberto Gonzalez (Hospital Interzonal de Agudos Evita, Avellaneda, PBA, Argentina), Romina Pratto (Sanatorio Anchorena Recoleta, CABA, Argentina), Patricio Gaggino (Sanatorio de Los Arcos, CABA, Argentina), Gimena Cardoso (Sanatorio Anchorena de San Martín, PBA, Argentina), Judith Sagardía (Hospital Nacional Dr. Alejandro Posadas, PBA, Argentina), Emilio Steinberg (Sanatorio Colegiales, CABA, Argentina), and Nahuel Dargains (HIEA y C San Juan de Dios, Buenos Aires, Argentina).

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Correspondence: Javier H Dorado PT, Elpidio Gonzalez 5350, ZIP1407 Buenos Aires, Argentina. E-mail: javierhdorado@gmail.com.

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in charge of data collection. Study data were collected and managed using REDCap electronic data capture tools hosted at Centro del Parque (Buenos Aires, Argentina), assuring the protection and confidentiality according to the Declaration of Helsinki. The subjects' information was acquired from the ICU admission to day 28 of mechanical ventilation or ICU discharge, whichever occurred first. All the investigation group members offered advisory and support through telephone or e-mail contacts.

Definitions

Weaning classification. The process of weaning from mechanical ventilation was classified according to 2 different definitions previously described.

International Conference Consensus (ICC) in Intensive Care published in 2007:[10]

1. *Simple weaning*: patients that were successfully extubated after the first separation attempt.
2. *Difficult weaning*: patients that failed the first separation attempt and required < 3 SBTs or < 7 d from the first SBT to be successfully extubated.
3. *Prolonged weaning*: patients that required > 3 SBT or > 7 d from the first SBT to be successfully extubated.

The Weaning according to a New Definition (WIND study) published in 2017:[11]

1. *Group 0 (no weaning)*: comprised patients who never experienced any separation attempt.
2. *Group 1 (short weaning)*: the first attempt resulted in a termination of the weaning process within one day (successful liberation or early death).
3. *Group 2 (difficult weaning)*: the weaning was completed after > 1 d but < 1 week after the first separation attempt (successful liberation or death).
4. *Group 3 (prolonged weaning)*: weaning continued 7 d after the first separation attempt (by successful liberation or death).

Spontaneous awakening trial definition. A spontaneous awakening trial was defined as the discontinuation of sedatives to determine whether the patient requires continued sedation or can be managed without sedation in the near future. We suggest performing an SAT on all patients who meet safety criteria.[13] The decision on the success or failure of the SAT was based on the clinical judgment of the health care team.

Spontaneous breathing trial definition. An SBT was defined as a formal test performed to assess the ability of a subject to be weaned from mechanical ventilation. We recorded the type of SBT (T-tube, pressure support ventilation [PSV] < 7 cm H_2O, PSV 0 cm H_2O and PEEP 0 cm H_2O, or CPAP) and the date when the first SBT was performed. The decision on the success or failure of the SBT was based on the clinical judgment of the health care team.

First separation attempt definition. The first separation attempt in intubated subjects was defined as when an SBT with or without extubation or a planned or unplanned extubation with or without SBT was performed. In tracheostomized subjects, the first separation attempt was computed as ≥ 24 h of spontaneous ventilation through tracheostomy without mechanical ventilation.[11]

Intubation to first separation attempt days. The number of days under invasive mechanical ventilation until the first separation attempt were registered.

Successful weaning. Successful weaning was considered when subjects remained alive without requiring invasive mechanical ventilation within the following 7 d of the attempted separation or were discharged from the ICU, whichever occurred first.[11]

Clinical outcomes. Extubation failure was defined as the need for re-intubation within 7 d following extubation.[23] The duration of mechanical ventilation and ICU length of stay were collected considering day 1 as the day in which the subject remained at least 12 h on mechanical ventilation and in the ICU, respectively. Status at ICU discharge or at day 28 from study inclusion (whichever occurred first) was classified as alive, dead, discharged to another health facility, or remained in ICU.

Statistical analysis. The variables are reported as mean (SD) or median (25–75 interquartile range [IQR]). Categorical variables are reported as the number of presentations (%). Shapiro-Wilk was used to test the distribution of the variables of interest. We used analysis of variance or Kruskal-Wallis rank-sum test to compare continuous variables among different weaning categories. Based on the binomial distribution, the 95% CI was estimated by the Agresti-Coull method for each mortality proportion after failing the first SBT. All the considered hypotheses were 2-tailed with a considered statistical significant P value < .05. Data processing was carried out with software R version 4.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

General Description of Participating ICUs

A total of 8 ICUs participated in the study, 4 belonging to the private health care system and 4 to the public health care system. Half of these ICUs are located in the

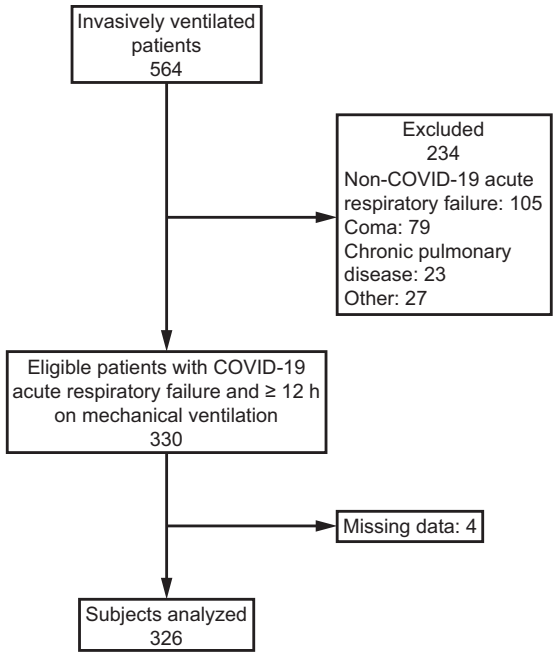

Fig. 1. Flow chart.

Autonomous City of Buenos Aires, whereas the other half are in the Buenos Aires province. The median [IQR] of ICU beds and ICU admissions per year was 16.5 [13.5–21.0] and 825 [630–925], respectively. During the data collection period, the median [IQR] of subjects admitted to each ICU was 44 [33–50]. Of all participating ICUs, 6 had formal protocols to guide both analgesia sedation and weaning from mechanical ventilation. The characteristics of the participating ICUs are shown in Table SM1 (see related supplementary materials at http://www.rcjournal.com).

Description of the Included Sample

Between April 1–August 31, 2020, of the 564 patients who required invasive mechanical ventilation, 129 did not meet the inclusion criteria, acute respiratory failure was not the indication for mechanical ventilation, and 135 whose acute respiratory failure was caused by factors other than COVID-19. Finally, 330 subjects with confirmed COVID-19 were included; and 4 of them were eliminated due to missing data, leaving 326 subjects for the primary analysis (Fig. 1). The median [IQR] age was 62 [52–70] y old, and most were male (67.8%) with a Simplified Acute Physiology Score II at the admission of 37 [29–46] and a Charlson comorbidity index of 2 [1–4]. The median [IQR] time from symptoms onset to intubation was 7 [4–9] d. The main characteristics of the sample are shown in Table 1.

Two hundred forty-six (75.4%) of the included subjects fulfilled Berlin ARDS criteria at any time during mechanical ventilation. Based on the Sequential Organ Failure Assessment score, the most frequent organ dysfunction (except respiratory failure) was the hemodynamic compromise ($n = 247$, 74.2%) (Table SM2, see related supplementary materials at http://www.rcjournal.com). The 28-d mortality was 55.5% ($n = 181$).

Table 1. Demographic Characteristics of Subjects With COVID-19

	Overall ($N = 326$)
Age, y	62 [52–70]
Male	221 (67.8)
BMI, kg/m^2	29.2 [26.2–33.9]
Charlson comorbidity index, points	2 [1–4]
SAPS II at ICU admission, points	37 [29–46]
SOFA day 1 of ventilation, points	5 [3–7]
P_{aO_2}/F_{IO_2} day 1 of ventilation	183 [137–245]
Symptoms onset to intubation, d	7 [4–9]
Outcomes	
Intubation to first SBT, d	8 [4.0–12.8]
Mechanical ventilation duration, d	12 [7–21]
Extubation	128 (40)
Re-intubation	38/128 (31.6)
ICU length of stay, d	16 [8–24]
Alive	121 (37.1)
Death	181 (55.5)
Still in ICU	8 (2.5)
Discharged to other health facility	16 (4.9)

Data are presented as median [interquartile range] or *n* (%).
BMI = body mass index
SAPS = Simplified Acute Physiology Score
SOFA = Sequential Organ Failure Assessment Score
SBT = spontaneous breathing trial

Weaning Process

During the study period, 153 subjects (46.9%) did not meet criteria for an SAT, whereas 170 (52.1%) did not experience any attempt of weaning from mechanical ventilation. In the remaining subjects, the first SBT had a median [IQR] duration of 40 [30–60] min and was successful in 103/150 (68.6%) subjects. Figure 2 shows the different SBT modalities used (Panel A) and the causes of failure (Panel B). Most of the subjects who failed the first SBT, 42/49 (89.4%), had a successful SBT during the ICU stay.

Among the subjects included in the study, 128 were extubated (120 planned and 8 unplanned extubations); 29.7% (38/128) were re-intubated during ICU stay (median of days to re-intubation 3 [1.5–9.0]), and these subjects had higher mortality (not re-intubated = 3.3% vs re-intubated = 36.8%, $P < .001$). The most frequent cause of re-intubation was the increase in the work of breathing ($n = 16$, 42.1%). Most of the re-intubated subjects were not extubated again ($n = 27$, 71.1%).

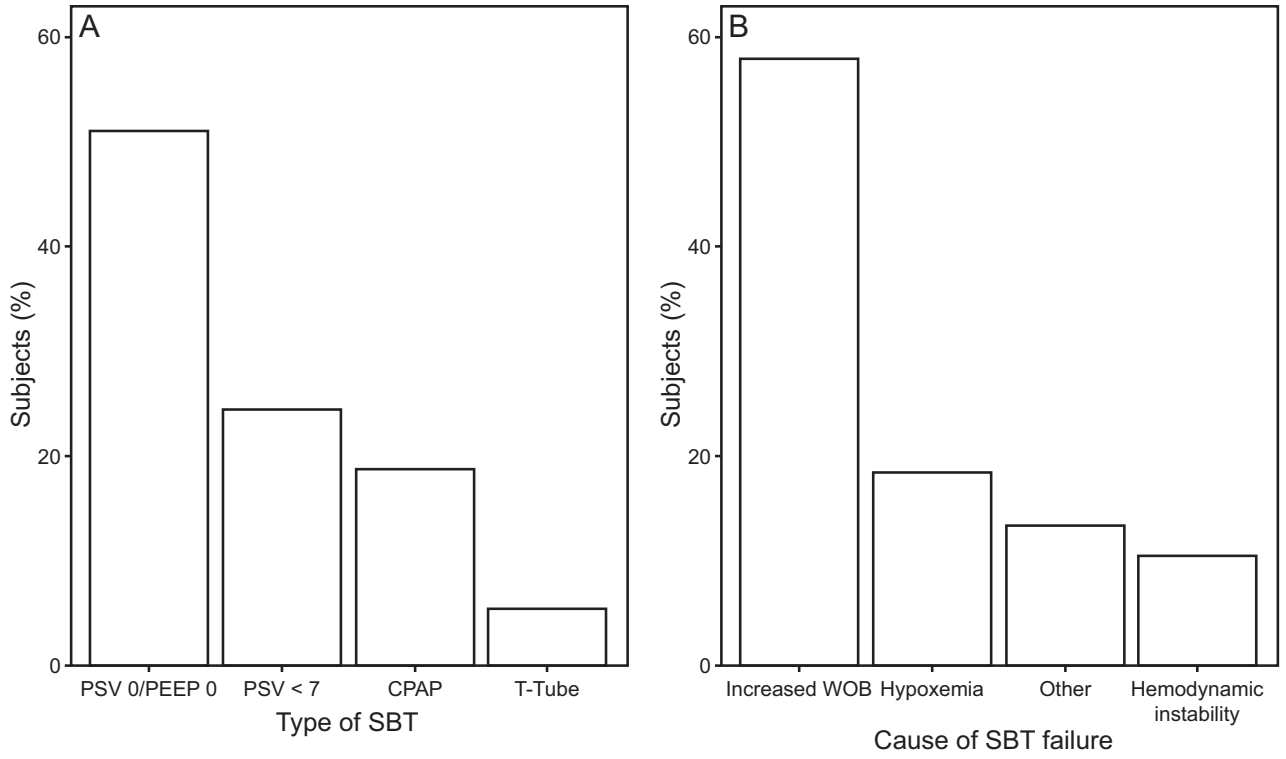

Fig. 2. Different spontaneous breathing trial modalities used (A) and the causes of failure (B). SBT = spontaneous breathing trial; PSV = pressure support ventilation.

A tracheostomy was performed in 78 participants (24%) with a median [IQR] of 16.5 [14.2–21.0] d of mechanical ventilation. Of these, 29 (37.2%) were successfully weaned from mechanical ventilation, and 8.9% (7/78) were decannulated in the ICU.

Classification of Subjects According to Weaning Criteria and Clinical Outcomes

Based on the ICC weaning criteria, 214 (65.6%) subjects could not be classified, as they either did not perform SBT during the ICU stay or initiated weaning after tracheostomy was performed. Of those that fit ICC criteria, 70 (62.5%), 22 (19.6%), and 20 (17.8%) subjects were classified as simple, difficult, and prolonged weaning, respectively. Clinical outcomes of each weaning category are shown in Table SM3[10] (See related supplementary materials at http://www.rcjournal.com).

Given the high proportion of subjects unable to be classified based on ICC criteria, the rest of the analysis was focused on WIND criteria.[11] Considering the WIND definition, the entire sample could be correctly classified:[11] group 0 = 52.1% (n = 170), group 1 = 28.5% (n = 93), group 2 = 8.0% (n = 26), group 3 = 11.3% (n = 37) (Figure 3). Table 2 shows the demographic and clinical characteristics at admission and the outcomes of each group. There were statistically significant differences in Charlson comorbidity index (P = .041), duration of mechanical ventilation (P < .001), and ICU length of stay among different weaning groups (P < .001).

Post Hoc Data Collection of non–COVID-19 Subjects

In order to perform a descriptive comparison, 89 subjects who required mechanical ventilation due to acute respiratory failure of non–COVID-19 etiology were included in the post hoc data collection. Although it is difficult to interpret due to the limited number of subjects analyzed, the time to first liberation attempt was 5 d shorter in this population. In addition, the duration of mechanical ventilation and ICU length of stay was also shorter. The WIND classification and clinical outcomes are summarized in Table SM4 (See related supplementary materials at http://www.rcjournal.com).

Discussion

This multi-center study provides relevant epidemiological information regarding weaning from invasive mechanical ventilation process in subjects with COVID-19. Our main findings can be summarized as follows: (1) Half of the included sample were never exposed to an SAT or formal attempts to wean from mechanical ventilation; (2)

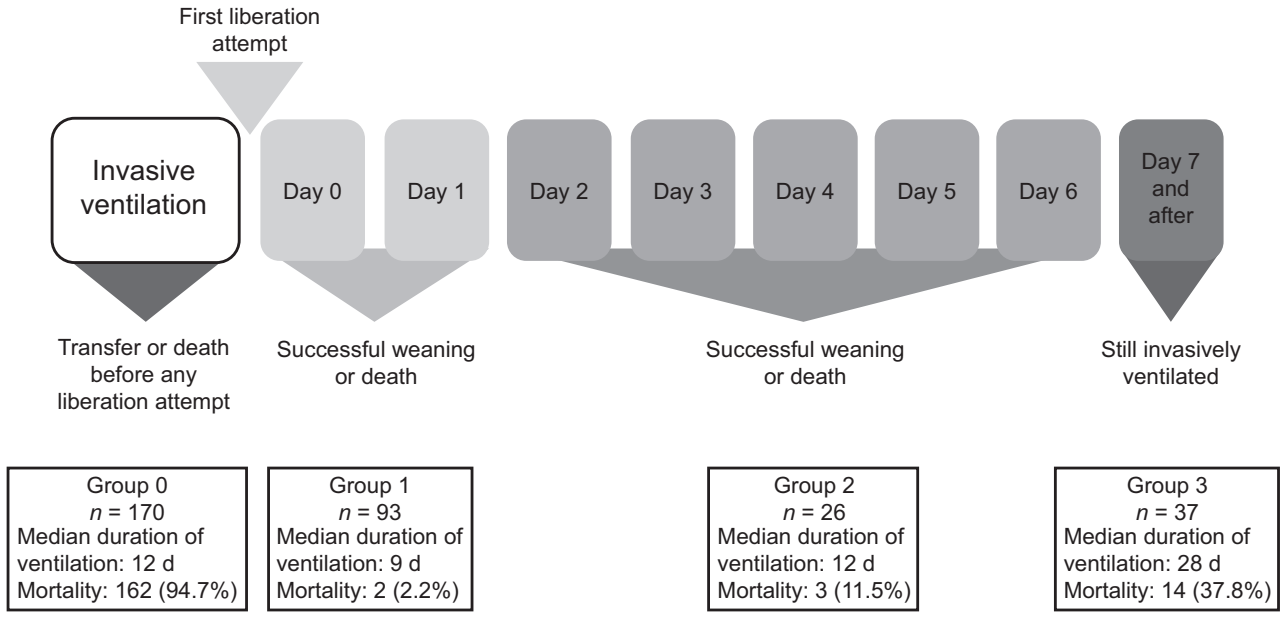

Fig. 3. Group classification according to the number of days between the first liberation attempt and the weaning termination.

Table 2. Subjects' Characteristics Based on Weaning According to a New Definition Classification

	Group 0 ($n = 170$)	Group 1 ($n = 93$)	Group 2 ($n = 26$)	Group 3 ($n = 37$)
Age, y	64.0 [56.3–70.0]	58.0 [45.0–67.0]	53.5 [48.5–63.8]	65.0 [57.0–70.0]
Male	111 (65.3)	67 (72.0)	18 (69.2)	25 (67.6)
Charlson comorbidity index, points	3.0 [1.0–4.0]	1.0 [0–2.5]	1.0 [0–2.0]	2.0 [1.0–4.0]
SAPS II at ICU admission, points	39.0 [31.0–52.5]	34.0 [26.5–41.5]	32.5 [28.0–41.0]	36.0 [29.0–44.0]
SOFA day 1 of ventilation, points	6.0 [4.0–7.0]	5.0 [3.0–7.0]	4.0 [3.0–6.0]	6.0 [4.0–8.0]
Symptoms onset to intubation, d	6.0 [3.0–9.0]	7.0 [4.0–9.0]	6.5 [4.2–8.7]	7.0 [5.0–9.0]
P_{aO_2}/F_{IO_2} day 1 of ventilation	166 [130–226]	208 [159–274]	206 [162–232]	196 [144–290]
Prone positioning sessions per subject, no.	2.0 [1.0–4.0]	2.0 [1.0–3.0]	1.0 [1.0–2.0]	2.0 [1.5–3.0]
Outcomes				
Intubation to first separation attempt, d		8.0 [3.5–13.0]	8.0 [6.0–10.0]	9.0 [6.0–14.0]
Mechanical ventilation duration, d	12.0 [7.0–20.0]	9.0 [4.0–18.0]	12.0 [9.0–15.0]	28.0 [17.0–37.0]
ICU length of stay, d	13.0 [7.0–20.0]	15.0 [9.0–26.0]	17.5 [13.0–22.8]	28.0 [21.0–43.0]
Extubation failure/extubation	0	2/79 (2.5)	9/22 (41)	27/27 (100)
Tracheostomy	33/170 (19.4)	15/93 (16.1)	5/26 (19.2)	25/37 (67.6)
Status at ICU Discharge or day 28				
Alive		87 (93.5)	20 (76.9)	14 (37.8)
Dead	162 (94.7)	2 (2.2)	3 (11.5)	14 (37.8)
Remain in ICU	1 (0.6)	3 (3.2)	2 (7.7)	2 (5.4)
Discharged to other health facility	7 (4.1)	1 (1.1)	1 (3.8)	7 (18.9)

Data are presented as median [interquartile range] or *n* (%).
SAPS = Simplified Acute Physiology Score
SOFA = Sequential Organ Failure Assessment

Fewer than one in 3 subjects were assigned to weaning group 1, according to the WIND definition; (3) Regardless of the weaning group, subjects with COVID-19 had a prolonged duration of mechanical ventilation; however, clinical outcomes in each group were similar to those obtained in non–COVID-19 subjects on mechanical ventilation admitted to the ICU at the same time; (4) Nearly half of the participants were extubated, and one third required

re-intubation; and (5) At the end of follow-up, only 42% of the sample were successfully weaned from mechanical ventilation.

Despite the clear benefits of the ABCDEF bundle, in our study, only 53.1% of subjects were exposed to an SAT, and < 50% performed an SBT.[15-17] This finding could be due to the decrease in adherence to clinical practice guidelines determined by the need to incorporate physicians with less training and experience in the management of ICU patients during the pandemic.[24] On the other hand, this finding could respond to the fact that a large number of subjects never met the clinical safety criteria for performing an SAT. It is even possible that the high number of subjects who were never exposed to SAT may in some way limit the correct interpretation of our findings, as the state of awareness is a determining variable for the decision to start an SBT. However, an international survey conducted during the pandemic identified respiratory and hemodynamic instability as the most frequent causes for which patients were unable to perform an SBT.[20] Consistent with this report, a high proportion of subjects in our cohort required prone positioning and had shock during their ICU stay. In summary, due to the characteristics and design of our study, it was not possible to confirm whether the cause for subjects not being exposed to an SAT indicates a worse quality of care or a characteristic of the clinical course of subjects with COVID-19.

The pandemic affected the distribution of subjects assigned to each weaning category. We found a clear reduction in subjects assigned to weaning group 1. As expected, we found the lowest mortality in this weaning category, even lower than that reported in the WIND study.[11] Another interesting finding of our study was that group 1 subjects had a prolonged duration of mechanical ventilation due to an increase in days to the first SBT. Three hypotheses could explain this. First, the stress generated in the health care system, the work load of health care professionals, and the need to incorporate additional physicians with short periods of training in the acquisition of skills could affect the quality of care and thus hinder the early identification of patients ready to be weaned from mechanical ventilation.[3,24] However, in non–COVID-19 subjects admitted to the ICU during the recruitment period of our study, the time to first weaning attempt was shorter (with a median of 3 d vs 8 d of mechanical ventilation). Second, in accordance with pre-pandemic recommendations the time to tracheostomy in our study was a median of 16.5 d; however, a recently published meta-analysis describes a reduction in days of mechanical ventilation in subjects undergoing early tracheostomy (< 14 d of mechanical ventilation).[25] Finally, the prolonged periods of systemic inflammation reported in patients with COVID-19 determine the development of organ failure that is difficult to resolve (especially pulmonary impairment) that could imply a longer time until patients are in adequate conditions to start the weaning process.[20,26] The high proportion of subjects included in our study with severe hypoxemia requiring prone positioning supports the latter hypothesis. However, despite the prolonged time on mechanical ventilation until the first SBT, with the potential risk of complications, the clinical outcomes of this group were similar to those reported by the WIND study.[11] It is likely that the weaning group to which subjects are assigned adequately reflects the clinical status at the time of starting this process regardless of the duration of previous mechanical ventilation.

Unlike the WIND study, where the "no weaning" group included 24.3% of the subjects, in our study it constituted > 50% of the sample; and in both cases, the mortality was markedly high. Furthermore, whereas in the WIND study the no weaning group had a median of 3 d of mechanical ventilation, we reported a 4-fold longer time on mechanical ventilation in our cohort of subjects with COVID-19.[11] This might be related to the findings reported by Estenssoro et al[3] in the SATICOVID study, who observed that the subjects that died did not have a rapid evolution; on the contrary, even on day 10 of mechanical ventilation, less than half of the subjects that finally did not survive had died at that time point. The higher rate of severe hypoxemia and a longer period of mechanical ventilation are likely due to the higher prevalence of comorbidities associated with chronic inflammation and not fully described mechanisms of lung inflammation.[26-28] In this scenario, the large proportion of subjects assigned to the weaning group 0 could be the determinants of the high mortality and low success rate in weaning in this cohort.

In our cohort, the re-intubation rate was considerably higher than reported in previous epidemiological studies carried out in heterogeneous populations of invasively ventilated subjects.[7] First, pneumonia as the main reason for mechanical ventilation has been demonstrated to increase the risk of extubation failure.[29] Second, the SBT modality most frequently reported in our country before the pandemic was T-tube;[9] however in our cohort of subjects with COVID-19, SBT types that provide low inspiratory support were used more frequently, which could lead to overestimating the ability of subjects to sustain spontaneous breathing after extubation, a situation that could have affected the results.[30,31] However, the latest weaning guidelines recommend using the SBT modality with inspiratory pressure augmentation since more patients can successfully overcome it, and it does not increase the risk of extubation failure.[32,33] Finally, the only study specifically designed to assess extubation failure in COVID-19 found similar results to ours.[21] It could be possible that high rates of extubation failure are a distinctive feature in these subjects. However, re-intubated subjects had higher mortality; therefore, we believe that future investigations should be conducted to assess interventions that reduce the incidence of re-intubation.

Our study has some limitations that should be addressed. The heterogeneity of daily practice in different hospitals and ICUs typically found in a multi-center study added to the possible modification of the usual practice in the work teams might jeopardize the generalizability of our results. However, most of the participating ICUs (6/8) had strict protocols of analgesia sedation and ventilator weaning, which allowed us to homogenize subjects' management and analyze the specific impact of COVID-19 on the weaning process beyond other possible confounders. Second, missing data in multi-center studies could be an important issue when assessing the validity and interpretation of the study results. To limit this barrier, we eliminated from the analysis those subjects with $> 10.0\%$ of missing data; and even in that situation, only 4 subjects were excluded. Third, given the study's main objectives, it was not planned to identify factors independently associated with outcomes.

Conclusions

The characteristics of the weaning process of mechanical ventilation were markedly affected by the COVID-19 pandemic. Most subjects never completed (or qualified for) a formal SBT and presented high mortality. Among the participants that formally initiated the ventilator liberation process, the duration of mechanical ventilation and ICU length of stay were longer than in previous studies; however, the clinical outcomes were similar to those reported in the weaning-related literature.

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