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Successful Versus Failed Transition From Controlled Ventilation to Pressure Support Ventilation in COVID-19 Patients: A Retrospective Cohort Study

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OBJECTIVES: In patients with COVID-19 respiratory failure, controlled mechanical ventilation (CMV) is often necessary during the acute phases of the disease. Weaning from CMV to pressure support ventilation (PSV) is a key objective when the patient's respiratory functions improve. Limited evidence exists regarding the factors predicting a successful transition to PSV and its impact on patient outcomes.

DESIGN: Retrospective observational cohort study.

SETTING: Twenty-four Italian ICUs from February 2020 to May 2020.

PATIENTS: Mechanically ventilated ICU patients with COVID-19-induced respiratory failure.

INTERVENTION: The transition period from CMV to PSV was evaluated. We defined it as "failure of assisted breathing" if the patient returned to CMV within the first 72 hours.

MEASUREMENTS AND MAIN RESULTS: Of 1260 ICU patients screened, 514 were included. Three hundred fifty-seven patients successfully made the transition to PSV, while 157 failed. Pao_2/Fio_2 ratio before the transition emerged as an independent predictor of a successful shift (odds ratio 1.00; 95% CI, 0.99–1.00; $p = 0.003$). Patients in the success group displayed a better trend in Pao_2/Fio_2, $Paco_2$, plateau and peak pressure, and pH level. Subjects in the failure group exhibited higher ICU mortality (hazard ratio 2.08; 95% CI, 1.42–3.06; $p < 0.001$), an extended ICU length of stay (successful vs. failure 21 ± 14 vs. 27 ± 17 d; $p < 0.001$) and a longer duration of mechanical ventilation (19 ± 18 vs. 24 ± 17 d, $p = 0.04$).

CONCLUSIONS: Our study emphasizes that the Pao_2/Fio_2 ratio was the sole independent factor associated with a failed transition from CMV to PSV. The unsuccessful transition was associated with worse outcomes.

KEYWORDS: acute respiratory distress syndrome; COVID-19; mechanical ventilation; respiratory effort; transition to pressure support ventilation

Mechanical ventilation plays a pivotal role in supporting lung function among critically ill patients suffering from respiratory failure (1). The need for invasive mechanical ventilation in COVID-19-induced acute respiratory distress syndrome (C-ARDS) is associated with ICU mortality ranging from 16% to 78% (2–7). Amid the pandemic, one of the focal research objectives was to gain a deeper understanding of how to effectively ventilate individuals with C-ARDS (8–10).

In the early phase of moderate to severe ARDS, controlled mechanical ventilation (CMV) manages respiratory drive and alleviates the workload on

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KEY POINTS

Question: To evaluate the risk factors associated with the failed transition from controlled to pressure support ventilation and the effect of a failed transition on the clinical outcome.

Findings: Pao_2/Fio_2 ratio was a predictor of a successful transition. Patients in the success group showed a better trend in Pao_2/Fio_2, $Paco_2$, plateau and peak pressure, and pH. The subjects in the failure group had higher ICU mortality, ICU length of stay, and duration of mechanical ventilation.

Meaning: A failure to transition from CMV to PSV is associated with worse clinical outcomes. The clinician should consider Pao_2/Fio_2, $Paco_2$, pH, plateau, and peak pressure during the transition.

respiratory muscles (11). However, it is important to note that CMV may potentially lead to adverse effects such as atelectasis, muscle atrophy, and diaphragm dysfunction (12–15). Weaning from CMV to pressure support ventilation (PSV) is a target to achieve as soon as the patient's respiratory function improves. During PSV, both the ventilator and the respiratory muscles provide forces to move air. Consequently, minute ventilation depends on the patient's trigger and efforts. The advantages of permitting spontaneous breathing through PSV are manifold, including reducing the need for sedation, safeguarding the diaphragm against atrophy, and enhancing ventilation–perfusion matching (16–18).

Timing is a critical factor in switching from CMV to PSV. A delayed transition may prolong the duration of mechanical ventilation, leading to extended ICU length of stay (ICU-LOS) and an elevated risk of complications and mortality (19–23). Conversely, initiating spontaneous breathing prematurely can also have adverse consequences, potentially resulting in derecruitment or the patient causing self-induced lung injury (P-SILI) (24, 25). Although limited evidence exists concerning the optimal timing and predictive variables for the transition to PSV, a recent study by Pèrez et al demonstrated that failure to transition from CMV to PSV following the initial spontaneous breathing trial is associated with prolonged ventilation, increased ICU stays, and heightened mortality rates (26, 27).

In this hypothesis-generating observational study focused on intubated COVID-19 patients experiencing respiratory failure, our objective is to identify predictors and early indicators of unsuccessful transitions from CMV to PSV and assess the outcomes of patients who experience such failures.

MATERIALS AND METHODS

Study Design

This retrospective cohort study analyzes data from a cohort included in an epidemiologic registry comprising 24 ICUs in Northern Italy (academic and nonacademic ICUs, all mixed surgical and medical, 2019nCOV_ICU, ClinicalTrial.gov: NCT04388670). Approval from each hospital's institutional review board was obtained for the registry, and due to the observational and emergency nature of the study, a waiver for written informed consent was granted. All procedures adhered to the ethical standards set forth by the responsible committee on human experimentation in accordance with the Helsinki Declaration of 1975.

Study Population

The 2019nCOV_ICU Registry includes ICU patients admitted from February 2020 to May 2020. Inclusion criteria consisted of confirmed severe acute respiratory syndrome coronavirus 2 infection, intubation, and mechanical ventilation. Patients were excluded if they had missing ventilatory parameters during the transition from CMV to PSV or if they did not undergo the switch from CMV to PSV. Further information about data collection is provided in the supplements.

The patients were managed according to the recommendations for COVID-19-induced acute respiratory failure.

Switching From CMV to PSV

CMV includes all ventilatory modalities in which the patient lacks respiratory drive due to sedation or muscle relaxation. These modalities include volume-controlled ventilation, pressure-controlled ventilation, and pressure-regulated volume-guaranteed ventilation. PSV is defined as a mode where the patient retains respiratory drive and effort, which are supported by the ventilator. As shown in **Figure 1**, we considered day 0 as the first day of PSV after

a phase of CMV. We defined the transition as a "failure of assisted breathing" if the patient had to be switched back to CMV within the first 72 hours.

When assessing clinical data before assisted breathing, we calculated the mean of days –2 and –1, whereas data following the transition to PSV were determined as the average of days 0 and +1. For our analysis, we categorized patients based on the timing of the transition, distinguishing between those for whom the transition occurred early (≤ 7 d of CMV) and those for whom it was late (> 7 d after CMV initiation). When examining predictors for mortality, we considered the ventilatory parameters recorded upon admission to the ICU.

Outcomes

The primary outcome of our study was to identify predictive factors associated with the failure to transition from CMV to PSV.

As for the secondary outcomes, we sought to determine whether this transition failure impacted the duration of mechanical ventilation or the ICU-LOS. We also examined whether there were differences in the trends of ventilatory parameters during the transition from CMV to PSV.

Statistical Analysis

Continuous variables are presented as mean (± SD) and median (interquartile ranges), with group comparisons performed using *T*-test or Wilcoxon-Mann-Whitney *U* test. Categorical variables are shown as absolute frequencies (percentages), compared using Chi-square or Fisher exact test.

A univariate logistic regression model assessed the association between failure and the parameters recorded before the transition, with significant parameters included in a backward/forward stepwise regression analysis to identify risk factors associated with failure probability. The odds ratio (OR) (95% CI) was used as a measure of association.

We used a linear mixed-effect model for repeated measures (with patients as random-effect and unstructured variance–covariance matrix) to evaluate whether the clinical parameters trend differs across the transition according to the outcome.

Survival analysis methods assessed the relationship between transition outcome (success-failure) and ICU mortality or the probability of being without ventilatory assistance over a 60-day follow-up. Kaplan-Meier curves were reported, and the Cox regression model was applied to estimate the hazard ratio (95% CI). The model for ICU mortality was adjusted for covariates detected through univariate logistic regression. Censored data were removed from the individuals still at risk. Statistical significance was defined as two-sided *p* values of less than 0.05. Statistical analysis was performed using Rstudio (Posit team (2023). Rstudio: integrated development Environment for R. Posit Software, PBC, Boston, MA).

RESULTS

The registry included 1260 critically ill COVID-19 patients across 24 ICUs. Of these, 746 patients were excluded due to missing data or a lack of transition from CMV to PSV. The remaining 514 patients from 22 institutions represent the study populations, with 357 patients (70%) succeeding and 157 (30%) failing the transition to PSV (**Supplemental material, Fig. 1**, http://links.lww.com/CCX/B305). During CMV, tidal volume averaged 7.1 ± 1. 3 mL/kg predicted body weight (PBW), with a driving pressure of 11 ± 3 cm H_2O, positive

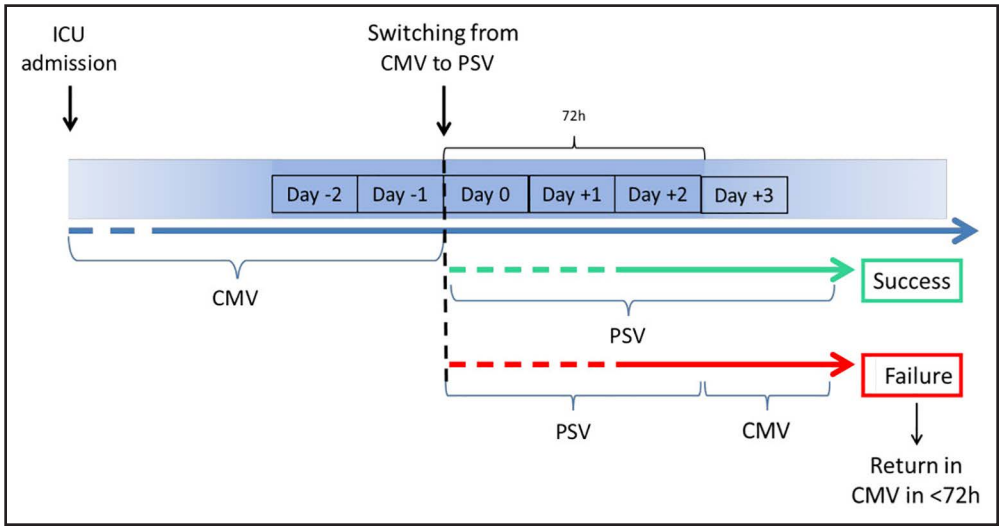

Figure 1. Timetable of the study. CMV = controlled mechanical ventilation, PSV = pressure support ventilation.

end-expiratory pressure (PEEP) 11 ± 3 cm H_2O, and a FIO_2 of 52% ± 13%. On the first day following the transition to PSV, the ventilation setting included a PEEP of 10.5 ± 2.5 cm H_2O, FIO_2 of 48% ± 12%, and pressure support of 11.8 ± 3.7 cm H_2O. Under these settings, the observed respiratory rate was 19 ± 4 breaths/min, plateau pressure 22.4 ± 4.4, and a tidal volume of 7.8 ± 1.6 mL/kg.

Cohort Demographics and Patient Respiratory Characteristics Before Switching From CMV to PSV

Baseline demographic data are summarized in **Table 1**. Approximately 24% were female, with an average age of 60 ± 11 years. The male sex and higher PBW were representative of the failure group ($p < 0.05$). Upon ICU admission, the ICU scores (Table 1) and disease severity, as indicated by ventilation support or oxygen supplementation ($p = 0.915$), were similar in both groups. The timing between the initiation of CMV and the transition to PSV showed no difference between the Successful and Failure groups (7 ± 6 vs. 7 ± 6 d, $p = 0.803$). Similarly, there were no differences in the duration of paralysis (5 ± 4 vs. 5 ± 5 d, $p = 0.466$) or the time spent in the prone position, which was approximately 2 days in both groups (**Supplements Table 1**, http://links.lww.com/CCX/B305).

Before transitioning from CMV to PSV, ventilatory settings were comparable between the groups, except for the FIO_2, which was lower in the Successful group than in the Failure group ($p = 0.016$). The PaO_2 over the FIO_2 (PaO_2/FIO_2) ratio and pH were significantly higher in the Successful group before the transition to PSV (**Table 2**), whereas the driving pressure was lower (10.7 ± 2.8 vs. 11.6 ± 3.1, cm H_2O, $p = 0.015$, $n = 274$). However, respiratory system compliance (C_{RS}) did not differ (44 ± 14 vs. 43 ± 15 mL/cm H_2O, $p = 0.514$, $n = 270$). We also noted that plateau pressure (which allows for comparable data evaluation when considering pressure and volume-control ventilation) was similar in both groups ($p = 0.069$).

In a multivariate logistic regression model adjusting for PaO_2/FIO_2 ratio, peripheral saturation of oxygen (SpO_2), pH, sex, and PBW, the best model for predicting the risk of failing the transition to PSV included the PaO_2/FIO_2 ratio,

TABLE 1.
Univariate Logistic Regression to Fail the Transition to Pressure Support Ventilation

Baseline Demographic Characteristics					
Demographics	**Global, *n* = 514**	**Success, *n* = 357**	**Failure, *n* = 157**	**OR (95% CI)**	***p***
Age (yr)	59.6 ± 10.8	59.7 ± 10.7	59.3 ± 11.0	1.00 (0.98–1.01)	0.682
Sex, female, *n* (%)	123 (24%)	95 (27%)	28 (18%)	0.6 (0.37–0.95)	0.033
Body mass index (kg/m²)	28.7 ± 5.52	28.9 ± 5.67	28.1 ± 5.1	0.97 (0.93–1.01)	0.128
Predicted body weight (kg)	66.6 ± 8.99	66.0 ± 8.72	67.9 ± 9.5	1.02 (1.00–1.05)	0.034
Clinical frailty scale	2.47 ± 1.14	2.51 ± 1.18	2.39 ± 1.06	0.91 (0.73–1.11)	0.356
Charlson comorbidity index	2.19 ± 1.65	2.18 ± 1.64	2.20 ± 1.68	1.01 (0.9–1.13)	0.891
Sequential Organ Failure Assessment Score	4.01 ± 1.41	3.97 ± 1.38	4.10 ± 1.48	1.07 (0.93–1.22)	0.333
Simplified Acute Physiology Score	36.0 ± 9.4	36.2 ± 9.7	35.7 ± 8.8	0.99 (0.97–1.01)	0.574
Acute Physiology and Chronic Health Evaluation II Score	10.3 ± 4.5	10.3 ± 4.6	10.4 ± 4.3	1.01 (0.97–1.05)	0.657
Comorbidities					
Cardiovascular disease (%)	65 (13%)	49 (14%)	16 (10%)	0.71 (0.38–1.27)	0.269
Pulmonary disease (%)	34 (7%)	21 (6%)	13 (8%)	1.44 (0.69–2.93)	0.316
Liver disease (%)	12 (2%)	11 (3%)	1 (1%)	0.20 (0.01–1.05)	0.127
Malignancy (%)	26 (5%)	16 (4%)	10 (6%)	1.45 (0.62–3.23)	0.371
Immunology disease (%)	55 (11%)	38 (11%)	17 (11%)	1.02 (0.54–1.84)	0.951
Others (%)	210 (41%)	149 (42%)	61 (39%)	0.89 (0.6–1.3)	0.540

OR = odds ratio.

TABLE 2.
Univariate Logistic Regression to Fail the Pressure Support Ventilation Trial

Ventilatory Characteristics Before Transition From Controlled Mechanical Ventilation to Pressure Support Ventilation					
Ventilatory Characteristics	**Global, *n* = 514**	**Success, *n* = 357**	**Failure, *n* = 157**	**OR (95% CI)**	***p***
Respiratory rate (breaths/min)	20.2 ± 4.3	20.2 ± 4.3	20.3 ± 4.2	1.01 (0.96–1.05)	0.728
F_{IO_2} (%)	52.3 ± 12.8	51.4 ± 12.2	54.3 ± 13.8	1.02 (1.00–1.03)	0.016
Positive End-Expiratory Pressure (cm H_2O)	11.5 ± 2.59	11.5 ± 2.52	11.5 ± 2.75	1.00 (0.93–1.08)	0.935
Pa_{O_2}/F_{IO_2} ratio (mm Hg)	193 ± 64.3	199 ± 63.7	177 ± 63.2	0.99 (0.99–1.00)	0.000
End-tidal CO_2 (mm Hg)	38.9 ± 8.70	39.5 ± 9.04	37.2 ± 7.43	0.97 (0.92–1.01)	0.182
pH	7.42 ± 0.06	7.42 ± 0.05	7.41 ± 0.07	0.96 (0.93–0.99)	0.011
Pa_{O_2} (mm Hg)	96.0 ± 31.9	97.9 ± 30.8	91.7 ± 34.1	0.99 (0.99–1.00)	0.044
Pa_{CO_2} (mm Hg)	49.6 ± 10.2	49.1 ± 9.76	50.7 ± 11.1	1.02 (1.00–1.03)	0.094
TV (mL)	464 ± 88.9	460 ± 88.3	473 ± 89.8	1.00 (1.00–1.00)	0.157
TV/predicted body weight (mL/kg)	7.1 ± 1.3	7.1 ± 1.3	7.0 ± 1.3	0.99 (0.83–1.17)	0.871
Peak pressure (cm H_2O)	26.4 ± 4.9	26.6 ± 4.8	26.0 ± 5.2	0.98 (0.90–1.05)	0.565
Plateau pressure (cm H_2O)	22.9 ± 3.1	22.7 ± 3.0	23.4 ± 3.2	1.08 (0.99–1.18)	0.069
Driving pressure (cm H_2O)	11.0 ± 2.9	10.7 ± 2.8	11.6 ± 3.2	1.11 (1.02–1.21)	0.018
Compliance respiratory system (mL/cm H_2O)	43.5 ± 14.4	43.9 ± 14.3	42.7 ± 14.6	0.99 (0.98–1.01)	0.514
Sp_{O_2} (%)	96.4 ± 2.3	96.6 ± 2.2	95.9 ± 2.5	0.88 (0.81–0.96)	0.002

OR = odds ratio, TV = tidal volume.

pH, and sex. However, only the Pa_{O_2}/F_{IO_2} ratio emerged as an independent predictor of successful transition (OR 1; 95% CI, 0.99–1.00; $p = 0.003$). By means receiver operator curve (ROC) analysis, we determined that a Pa_{O_2}/F_{IO_2} ratio of 187 mm Hg represented the best cutoff point for predicting the successful transition to PSV (**Supplemental material, Fig. 2**, http://links.lww.com/CCX/B305), albeit the area under the curve is low, highlighting the limited predictive value of the sole Pa_{O_2}/F_{IO_2}. When incorporated into the multivariable logistic regression, driving pressure became one of the two independent variables (OR 1.16; 95% CI, 1.05–1.28; $p = 0.003$), along with female sex (OR 0.30; 95% CI, 0.13–0.63; $p = 0.002$), associated with the failure to transition to the PSV. However, due to the high rate of missing driving pressure values ($n = 241$), those data should be carefully evaluated due to the high risk of selection bias.

Patient Characteristics After Switching From CMV to PSV

Following the shift from CMV to PSV, patients in the Success group exhibited a decreased requirement for F_{IO_2} (46 ± 11 vs. 54 ± 13, $p < 0.001$) and PEEP (10 ± 2 vs. 11 ± 3, $p < 0.001$, **Table 3**). In the first 48 hours posttransition, the Success group showed an improvement in the Pa_{O_2}/F_{IO_2} ratio, whereas it deteriorated in the Failure group (**Fig. 2*A***, p group × time < 0.001). Additionally, the reduction in Pa_{CO_2} was more pronounced in the Successful group compared with the Failure group (**Fig. 2*B***, p group × time < 0.001), with a pH that was significantly higher in the Successful group after the transition to PSV (7.45 ± 0.05 vs. 7.42 ± 0.06, $p < 0.001$). Peak inspiratory pressure also decreased more in the Successful group. Similarly, despite being measured in a limited number of patients, plateau pressure decreased to 22 ± 3 cm H_2O in the Successful group while it increased to 23 ± 4 cm H_2O in the Failure group. Respiratory rate, C_{RS}, and PMI were comparable between the groups within 48 hours following the transition to PSV.

When patients were categorized into early (≤ 7 d) or late (> 7 d) transition, the variables associated with failure were comparable between these subgroups (**Supplements Tables 2** and **3**, http://links.lww.com/CCX/B305). In the Successful group with an early

TABLE 3.
Ventilator Settings and Respiratory Mechanics After Switching From Controlled Mechanical Ventilation to Pressure Support Ventilation

Ventilatory Characteristics After Transition From Controlled Mechanical Ventilation to Pressure Support Ventilation				
Ventilatory Characteristics	**Global, *n* = 514**	**Success, *n* = 357**	**Failure, *n* = 157**	***p***
F_{IO_2} (%)	48 ± 12	46 ± 11	54 ± 13	< 0.001
Positive end-expiratory pressure (cm H_2O)	10.5 ± 2.5	10.2 ± 2.4	11.2 ± 2.8	< 0.001
Respiratory rate (breaths/min)	19 ± 4	18 ± 4	19 ± 4	0.105
P_{aO_2}/F_{IO_2} ratio (mm Hg)	195 ± 62	206 ± 60	169 ± 57	< 0.001
Tidal volume/predicted body weight (mL/kg)	7.8 ± 1.6	7.9 ± 1.6	7.6 ± 1.6	0.088
Peak pressure (cm H_2O)	22.4 ± 4.4	21.7 ± 4.0	24.0 ± 4.9	< 0.001
Plateau pressure (cm H_2O)	22.9 ± 3.6	21.9 ± 3.4	24.1 ± 3.5	< 0.001
Driving pressure (cm H_2O)	11.7 ± 3.6	11.2 ± 3.5	12.3 ± 3.6	0.077
Compliance respiratory system (mL/cm H_2O)	46 ± 18	47 ± 17	44 ± 20	0.233
Pmusc Index (cm H_2O)	1.4 ± 2.1	1.3 ± 2.0	1.7 ± 2.3	0.296
End-tidal CO_2 (mm Hg)	39 ± 9	39 ± 8	41 ± 10	0.404
pH	7.44 ± 0.05	7.45 ± 0.05	7.42 ± 0.06	< 0.001
P_{aCO_2} (mm Hg)	48 ± 9	47 ± 8	51 ± 10	< 0.001
Ventilatory ratio (mL*mm Hg/min*kg)	1.81 ± 0.70	1.76 ± 0.55	1.85 ± 0.61	0.190
Minute ventilation (L/min)	9.3 ± 2.6	9.3 ± 2.7	9.3 ± 2.4	0.998
Dead space fraction (%)	19.3 ± 12.1	19.2 ± 13.9	19.5 ± 10.7	0.913

transition, F_{IO_2} and plateau pressure were lower, whereas S_{pO_2}, P_{aO_2}/F_{IO_2} ratio, and pH showed significantly higher values when compared with the Failure group (Supplements Tables 2 and 3, http://links.lww.com/CCX/B305). In the subgroup of patients with late transition from CMV to PSV (> 7 d), the P_{aO_2}/F_{IO_2} ratio was significantly higher in the Successful group.

Clinical Outcomes

The overall ICU mortality was 21.4%. Subjects in the Failure group exhibited a higher risk of ICU mortality at 60 days compared with the Successful group (unadjusted HR 1.84; 95% CI, 1.26–2.69; p = 0.002, **Fig. 3**). The increased risk of ICU mortality persisted even after adjusting for other confounders (age, Charlson comorbidity index, Simplified Acute Physiology Score [SAPS], Acute Physiology and Chronic Health Evaluation [APACHE II] Score, pH, and P_{aCO_2} at admission), revealing an aHR of 2.08 with a 95% CI of 1.42–3.06, p value of less than 0.001. The average ICU-LOS was 23 ± 15 days, with a significant difference between the Success and Failure groups (21 ± 14 vs. 27 ± 17 d, $p < 0.001$). The duration of mechanical ventilation was longer (19 ± 18 vs. 24 ± 17, p = 0.04) in the Failure group, along with a reduced probability of breathing without assistance in comparison to the Success group (HR 0.54; 95% CI, 0.39–0.76; $p < 0.001$).

DISCUSSION

In this retrospective cohort study involving 514 COVID-19 patients on mechanical ventilation, we found that only P_{aO_2}/F_{IO_2} was independently associated with an unsuccessful transition from CMV to PSV. A failed transition was independently associated with the worst clinical outcomes.

PSV has been shown to be helpful as a ventilation mode in the acute phase of pulmonary dysfunction (23, 28, 29). Early initiation of spontaneous breathing may be associated with multiple benefits (16, 30, 31). The switch from CMV to PSV represents a critical moment as it may lead to the development of injurious

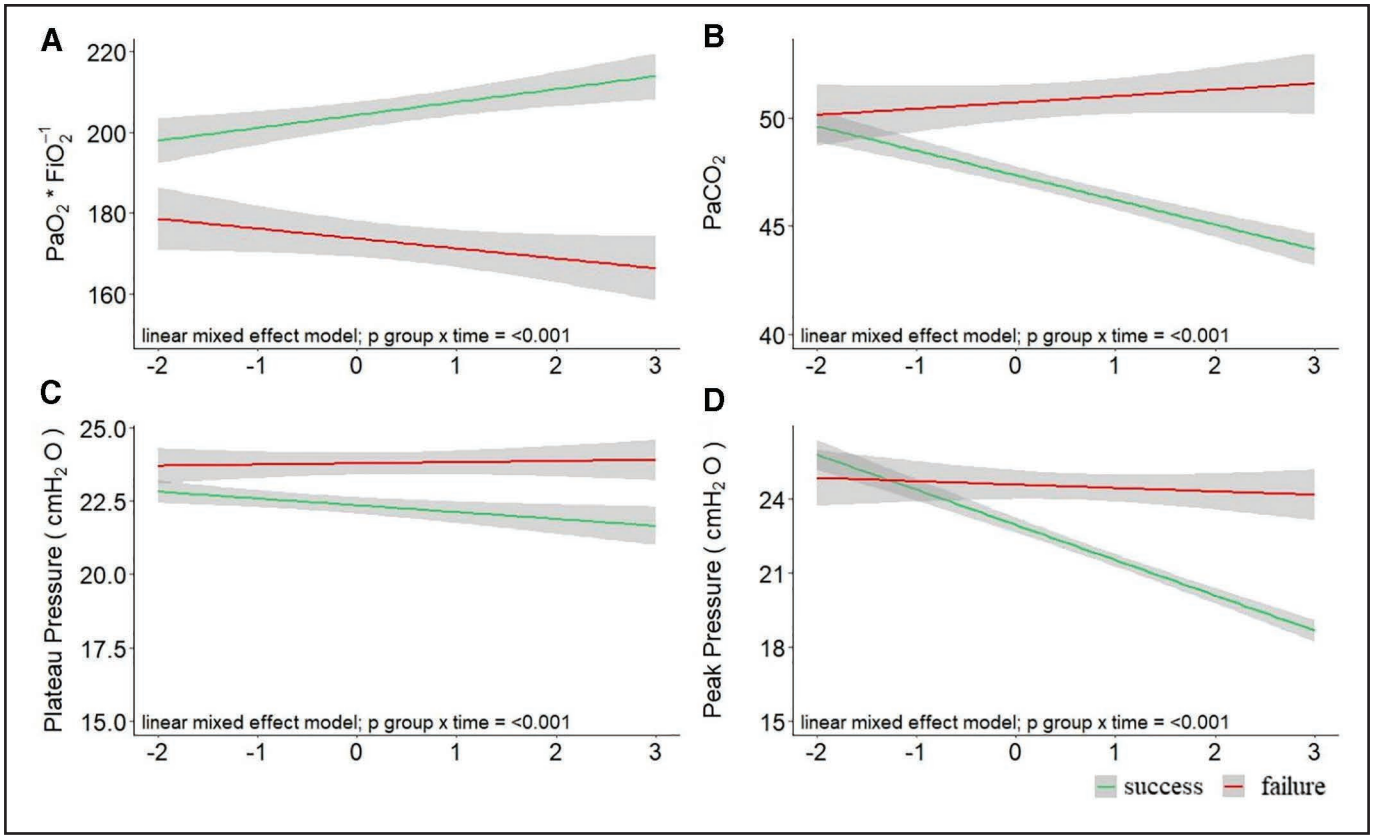

Figure 2. Linear mixed model with patients as random effects: **A**, Pao2/Fio2; **B**, Paco2; **C**, peak inspiratory pressure; and **D**, plateau between the success and the failure group. The entire models for all the variables are inserted in the supplements, section "Models for Pao_2/Fio_2, $Paco_2$, peak inspiratory pressure, and plateau pressure."

ventilation, damaging the lungs or the diaphragm (25, 32). Multiple systems have been developed to monitor and optimize spontaneous breathing patients, including esophageal pressure, occlusion maneuvers, diaphragm electrical activity, and ultrasound (33). However, it is essential to apply these measurements with consideration of the clinical context. In the upcoming paragraphs, we discuss the three main findings from this study.

First, our population transitioned to PSV after approximately 7 days of CMV, with no distinction between those who succeeded and those who failed. Age, comorbidities, and severity scores (SAPS, APACHE II, and Sequential Organ Failure Assessment) did not show any correlation with the transition outcome. These findings align with the analysis by Glover et al (24), which identified factors associated with a failed transition to PSV. In our study, females with lower PBW and subjects with higher Pao_2/Fio_2 ratio, Spo_2, pH, and lower driving pressure were more likely to succeed in the transition to PSV. In their recent study, Pèrez et al (27) reported similar results, with higher Pao_2/Fio_2 (OR 0.87) and pH (OR 0.61) correlating with effective transitions from CMV to PSV. In our multivariate analysis, only Pao_2/Fio_2 remained correlated with successful transitions. A lower Pao_2/Fio_2 ratio may indicate an insufficiently healed lung not ready for further weaning, as might a higher driving pressure. No established threshold for Pao_2/Fio_2 ratio exists for transitioning from CMV to PSV. Although a Pao_2/Fio_2 ratio greater than 150 mm Hg (20) is often considered to attempt discontinuation of mechanical ventilation, our study found that Pao_2/Fio_2 averaged 177 ± 63 mm Hg and 199 ± 64 mm Hg in the failed and successful groups, respectively. According to the ROC analysis performed, we propose that a threshold of 187 mm Hg might be considered for the transition from CMV to PSV, albeit this threshold should be further validated, and the low sensitivity and specificity highlights that other factors should be taken into account.

Second, patients in the Success group required less Fio_2 and PEEP after transitioning to PSV. The Successful group exhibited higher Pao_2/Fio_2 levels and pH, and lower $Paco_2$, plateau, and peak

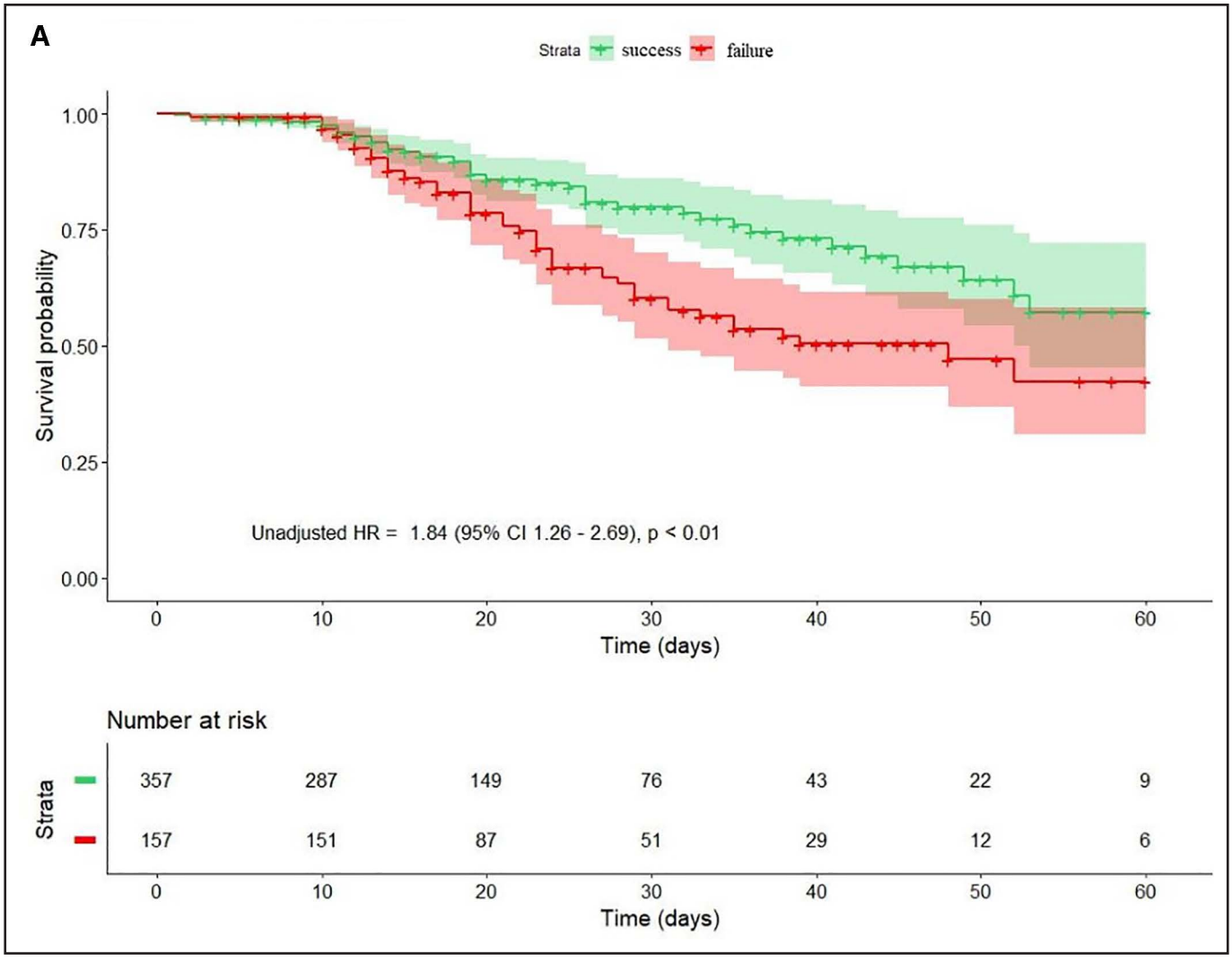

Figure 3. A, Kaplan-Meier ICU mortality, hazard ratio (HR) between the success and the failure group. The adjusted model is in the supplements section "adjusted model for ICU survival."

pressures, throughout the transition. Esnauld et al (34) demonstrated that mechanically ventilated COVID-19 patients who fail the transition to PSV often present excessive respiratory efforts, indicated by increased occlusion pressure at 100 ms (P0.1) and end-expiratory occlusion pressure (ΔPocc). This again suggests that patients who fail may have lungs that are not fully recovered and that PSV might exacerbate the condition, leading to P-SILI. Patients who successfully transitioned also had better lung function starting from 2 days before, evidenced by the Pao_2/Fio_2, $Paco_2$, plateau, and peak pressure, showing a lung ready to be weaned to a more physiologic type of ventilation. Our data align with a previous report by Cereda et al (35) on 58 patients. Despite not being statistically significant, they observed a trend to a higher Pao_2/Fio_2 in patients who were successfully transitioned (218 ± 68 vs. 233 ± 72) with a decrease in Pao_2/Fio_2 in patients who failed (181 ± 67 vs. 159 ± 62). In the same way, the $Paco_2$ and peak inspiratory pressure showed a lower level in the patients who successfully transitioned to PSV, representing an improved lung.

Third, failing to transition to PSV was associated with worse clinical outcomes. It increased the risk of 60-day ICU mortality (adjusted HR 2.08) and reduced the likelihood of breathing without assistance (HR 0.54), corroborating previous data (ICU mortality Relative Risk 2.9; 95% CI, 1.46–5.94) and aligning with recent publication by Pèrez et al (23, 24, 27). However, our study cannot definitively determine whether the failure in the PSV trial contributes to adverse

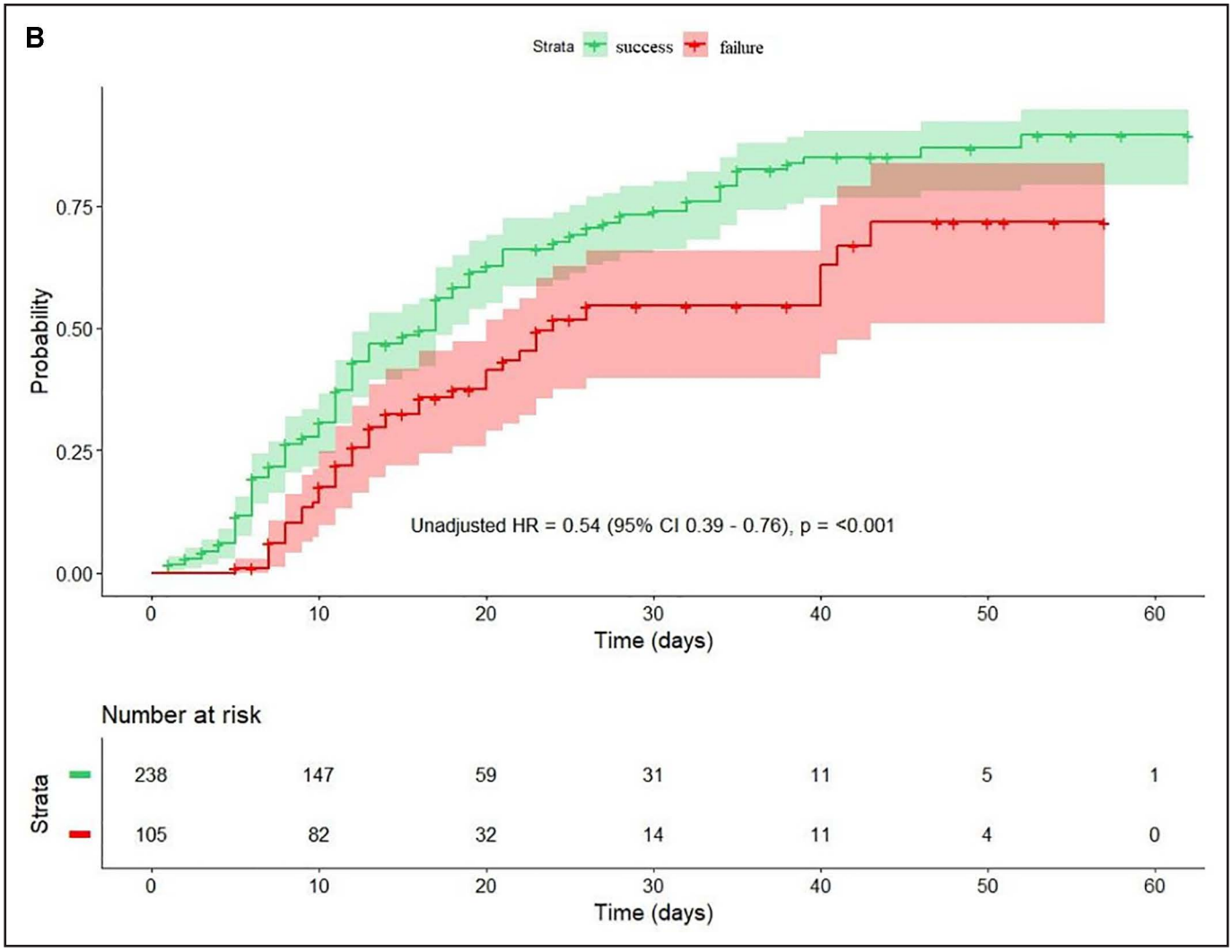

Figure 3. B, Kaplan-Meier probability of breathing without assistance, hazard ratio between the success and the failure group.

outcomes or merely serves as a marker of worsened lung condition.

A key approach toward an optimal ventilator weaning process should be focused on the proper timing of the patient's readiness, which should not primarily rely on timing (we did not find any difference from patients weaned before or after 7 d). A careful evaluation should include Pao_2/Fio_2, pH, sex, and driving pressure as key prognostic factors besides other factors such as PEEP, minute volume ventilation, and possibly mechanical power. Additionally, advanced monitoring of the patient's effort should be considered. During the transition, clinicians should monitor Pao_2/Fio_2, $Paco_2$, plateau, and peak inspiratory pressure as early indicators of a failed switch. It is essential to strike a balance, as both delayed weaning and a failed transition have their respective negative consequences and should be avoided.

Our study presents several limitations. Its observational and retrospective design precludes establishing any causal relationship. Furthermore, the study's retrospective nature, which foresaw only one data point collection per day, did not allow us to capture if any intermediate step was performed which was the goal of single centers when adjusting the ventilator. We did not evaluate the time from the onset or hospitalization of the symptoms to the transition from CMV to PSV. The transition to PSV and the criteria for returning to CMV were not standardized, representing the most significant limitation of our study. Our focus on respiratory parameters should be considered in the context of other potential influencing factors (24). Lastly, we lacked data on respiratory drive and inspiratory efforts during the transition to PSV, which could have provided further insights into the mechanism of failed transitions (36, 37).

CONCLUSIONS

A significant knowledge gap exists regarding the correct timing for the switch from CMV to PSV in patients with respiratory failure. Our study highlights the importance of considering Pao_2/Fio_2, pH, sex, and driving pressure as predictive markers for an elevated risk of transition failure. Failing to switch to PSV was linked with poorer clinical outcomes, although the exact causal relationship between these factors warrants further investigation.

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