

# Prognostic factors and outcomes in COVID-19 patients requiring prolonged mechanical ventilation: a retrospective cohort study

Roman Melamed<sup>1</sup>, Francisco Paz, Stacy Jepsen, Claire Smith, Ramiro Saavedra, Maximilian Mulder, Adnan Masood, Joshua Huelster, Lisa Kirkland, Alena Guenther and Lori Boland

## Abstract

**Background:** Mechanical ventilation (MV) in coronavirus disease 2019 (COVID-19) patients is associated with high mortality and extensive resource utilization. The aim of this study was to investigate prognostic factors and outcomes associated with prolonged mechanical ventilation (PMV) in COVID-19 patients.

**Methods:** This was a retrospective cohort study of COVID-19 patients requiring invasive MV who were hospitalized between 1 March 2020 and 30 June 2021 in the intensive care units (ICUs) of three referral hospitals belonging to a single health system. Data were extracted from electronic health records. PMV was defined as > 17 days of MV.

**Results:** Of 355 patients studied, 86 (24%) required PMV. PMV patients had lower PaO<sub>2</sub>/FiO<sub>2</sub> ratio, higher PCO<sub>2</sub>, and higher plateau and driving pressures during the first 2 weeks of MV than their short MV (SMV; ≤ 17 days) counterparts. PMV patients received more proning, neuromuscular blockade, and tracheostomy, had longer ICU and hospital length of stay (LOS), and required discharge to an inpatient rehabilitation facility more frequently (all *p* < 0.001). Overall 30-day mortality was 43.9%, with no statistically significant difference between PMV and SMV groups. In PMV patients, smoking, Charlson comorbidity index > 6, and week 2 PaO<sub>2</sub>/FiO<sub>2</sub> ratio < 150 and plateau pressure ≥ 30 were positively associated with 30-day mortality. In a multivariate model, results were directionally consistent with the univariate analysis but did not reach statistical significance.

**Conclusion:** PMV is commonly required in COVID-19 patients with respiratory failure. Despite the higher need for critical care interventions and LOS, more than half of the PMV cohort survived to hospital discharge. Higher PaO<sub>2</sub>/FiO<sub>2</sub> ratio, lower plateau pressure, and fewer comorbidities appear to be associated with survival in this group.

**Keywords:** COVID-19 virus disease, intensive care units, length of stay, mechanical ventilation, respiratory failure

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## Introduction

Respiratory failure requiring mechanical ventilation (MV) in coronavirus disease 2019 (COVID-19) patients is associated with high mortality, and additional research is necessary to understand outcomes and guide therapies.<sup>1</sup> COVID-19 patients

with respiratory failure frequently require prolonged MV (PMV) support. In a retrospective study of 553 ventilated COVID-19 patients, the median duration of MV was 13.5 days (interquartile range (IQR) = 7.5–22.5) overall, and 16.5 days (IQR = 10.5–26.5) in those surviving to intensive

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care unit (ICU) discharge.<sup>2</sup> In a large international COVID-19 registry report, the median duration of MV was 8.8 days, with an IQR of 3.3–17 days.<sup>3</sup>

In general, PMV has been associated with poor outcomes and high rates of healthcare resource utilization. In a multi-center study of 260 adult patients who received at least 21 days of MV due to acute illness, 1-year mortality was 48%.<sup>4</sup> In a prospective study of medical, surgical, and trauma patients requiring PMV, 1-year mortality was over 50%, with vasopressor requirements, hemodialysis, thrombocytopenia and age > 50 identified as independent predictors of death.<sup>5</sup> In a meta-analysis of outcomes in patients requiring PMV, mortality at hospital discharge and at 1 year were 29% and 62%, respectively, only 19% were discharged to home, and only 50% were successfully liberated from MV.<sup>6</sup> Outcomes after PMV appear to be significantly worse than expected by patients' surrogates and physicians.<sup>7</sup>

Factors associated with disease progression and mortality in COVID-19 patients have been identified and include older age, prior dependency, immunocompromised state, organ dysfunction, and an increased number of organ support therapies.<sup>3,8–11</sup> At the same time, information on factors predisposing to PMV and its outcomes in COVID-19 patients is very limited. One report using 28 days of MV as a threshold identified older age and sequential organ failure assessment (SOFA) score at ICU admission, lower PaO<sub>2</sub>/FiO<sub>2</sub> ratio, and respiratory system compliance during the first 5 days of MV, need for renal replacement therapy, ventilator-associated pneumonia, and cardiovascular complications as risk factors for PMV.<sup>12</sup> However, it is not clear whether previously published data are universally applicable to all treatment settings due to the variability in patient populations, geographic area, and time of disease development.<sup>13,14</sup>

This study focuses on prognostic factors and outcomes in COVID-19 patients who required PMV. While PMV definitions used in the literature are variable and depend on the patient population, no definition specific to COVID-19 patients with respiratory failure has been developed.<sup>15–17</sup> A threshold of > 17 days corresponds to greater than the 75th percentile of MV duration among COVID-19 patients in the Society of Critical Care Medicine's (SCCM) Global Viral Infection and Respiratory Illness Universal Study (VIRUS)

COVID-19 Registry, and was chosen for this report to reflect real-world COVID-specific data.<sup>3</sup>

## Materials and methods

### Study design and setting

We performed a retrospective cohort study at three referral hospitals belonging to a single, large healthcare system in Minnesota, USA with a combined 143 adult ICU beds and uniform treatment protocols. The study protocol was approved by the Allina Health Institutional Review Board (#1653821-8) with a waiver of informed consent.

### Patients

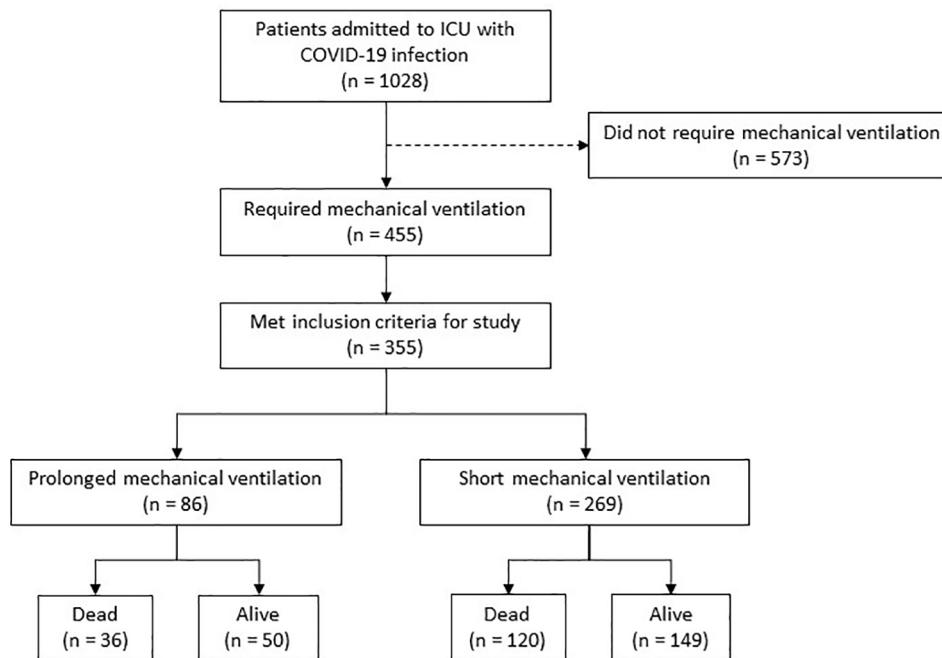
The initial cohort comprised patients who were hospitalized with a COVID-19 infection and required invasive MV between 1 March 2020 and 30 June 2021. Patients were then excluded if they were < 18 years of age, received treatment with extracorporeal membrane oxygenation (ECMO), or if they did not provide consent for use of their medical record data for research. Patients whose care was withdrawn within the first 48 h of MV per healthcare directives, and those with a cause of death unrelated to COVID-19 pneumonia were also excluded.

### Data source

Data were extracted from the electronic health record at participating hospitals. In addition, two investigators (R.M., F.P.) conducted reviews of medical charts to confirm early withdrawal of care and determine cause of death, including adjudication to reach consensus as needed.

### Definitions and outcomes

PMV was defined as > 17 days of ventilator support, and short duration of MV (SMV) was defined as ≤ 17 days of ventilator support. Baseline patient characteristics included demographics and pertinent medical history. The Charlson comorbidity index (CCI) was computed based on components of medical history as previously described.<sup>18</sup> Respiratory measures included partial pressure of arterial oxygen to the fraction of inspired oxygen ratio (PaO<sub>2</sub>/FiO<sub>2</sub>), partial pressure of carbon dioxide (PCO<sub>2</sub>), plateau pressure, and driving pressure calculated as a difference between plateau and positive end-expiratory



**Figure 1.** Flow diagram of patients and 30-day mortality.

pressures, and were analyzed using the most extreme values recorded in week 1 and week 2 after the start of MV. Treatment-related variables that were examined included proning, dialysis, the administration of neuromuscular blockade, steroids and vasopressors, and tracheostomy.

The primary outcome was 30-day mortality. Secondary outcomes included 60- and 90-day mortality, ICU and hospital length of stay (LOS), and MV days, discharge status and discharge destination in PMV patients.

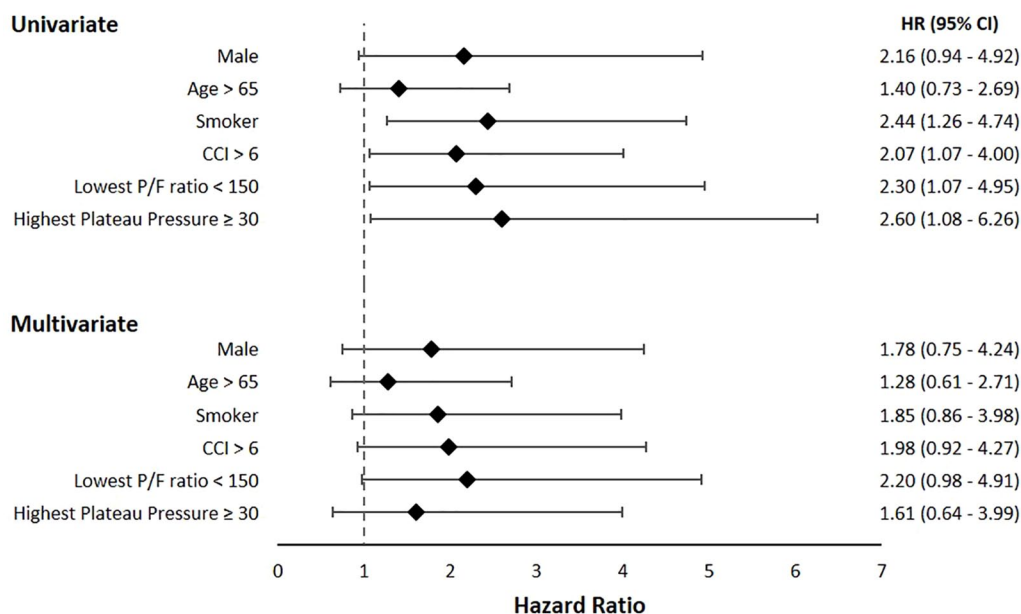
### Statistical analysis

Descriptive statistics included counts and proportions for categorical variables, and mean ( $\pm$  standard deviation) or median (IQR) for continuous variables. Comparisons between the PMV and SMV groups were assessed using *t*-tests or Wilcoxon rank sum tests for continuous variables, and chi-square or Fisher's exact tests for categorical variables as appropriate. Similar methods were used to compare the values of patient characteristics, clinical history, respiratory parameters, treatments, and outcomes by 30-day mortality status within the PMV group. Univariate and multivariate Cox proportional hazards regression modeling was performed to identify factors associated with 30-day

mortality in patients with PMV, with hazard ratios (HRs) and 95% confidence intervals (CIs) used to quantify the magnitude and direction of association. For purposes of regression analysis, the following continuous variables were dichotomized as follows: age ( $\leq 65$ ,  $> 65$ ), CCI ( $\leq 6$ ,  $> 6$ ), lowest week 2 PaO<sub>2</sub>/FiO<sub>2</sub> ratio ( $< 150$ ,  $\geq 150$ ), and highest week 2 plateau pressure ( $< 30$ ,  $\geq 30$ ). Cox analysis results were illustrated using forest plots. Statistical analysis was conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC)

### Results

Among 455 patients with confirmed COVID-19 infection who required MV during the study timeframe, 355 met inclusion criteria and were included in analysis (Figures 1). The median age in the study cohort was 65 years, 59% were male, and 86 (24%) required PMV (Table 1). In comparing baseline characteristics of patients in the PMV and SMV groups, patients requiring PMV were more likely to be male ( $p=0.03$ ), Hispanic ( $p=0.005$ ), and to be admitted directly to the ICU from an outside hospital ( $p=0.035$ ) than their SMV counterparts. Patients in the PMV group also had fewer comorbidities than the SMV patients, which is reflected by their lower median CCI ( $p=0.027$ ).



**Figure 2.** Prognostic factors for 30-day mortality among patients with prolonged mechanical ventilation from univariate and multivariate Cox proportional hazards regression analysis. Multivariate model included all variables shown. Respiratory parameters reflect extremes recorded in week 2 of mechanical ventilation. CCI, Charlson comorbidity index; CI, confidence interval; HR, hazard ratio; P/F,  $\text{PaO}_2/\text{FiO}_2$ .

With regard to respiratory parameters, patients with PMV generally had lower median  $\text{PaO}_2/\text{FiO}_2$  ratio, higher median  $\text{PCO}_2$ , and higher plateau and driving pressures during the first 2 weeks of MV as compared with those with SMV (Table 2). PMV patients required more critical care interventions, including prone positioning, neuromuscular blockade, and tracheostomy (all  $p < 0.001$ ). Median time from the initiation of MV to tracheostomy was 28 days (IQR: 18.0–28.1). The need for hemodialysis was more frequent in the PMV group, but the difference was not statistically significant. As expected, MV duration and ICU and hospital LOS were longer in the PMV group, and significantly more PMV patients required discharge to an inpatient rehabilitation facility ( $p < 0.001$  for all). Thirty-day mortality was not significantly different for PMV *versus* SMV patients (41.9% *versus* 44.6%, respectively,  $p = 0.66$ ), and 60- and 90-day mortality were also similar in the two groups. Review of patient medical records revealed that while progressive respiratory failure and multisystem organ failure were the most common causes of death in both groups, patient healthcare directives and non-COVID-19-related comorbidities leading to a generally poor prognosis prompted a withdrawal of care in 18 of the 120 patients (15%) in the SMV group who did not survive to 30 days.

Of the 86 patients who received PMV, 50 (58%) were alive at 30 days (Table 3). PMV survivors had significantly more ventilator days and longer ICU and hospital LOS than non-survivors. Male sex, lower body mass index (BMI), a history of smoking, a higher median CCI, lower  $\text{PaO}_2/\text{FiO}_2$  ratio, and higher plateau pressure in week 2 were associated with mortality in PMV patients, while tracheostomy placement was associated with survival. As compared with non-survivors, survivors had lower week 2 plateau pressure and higher  $\text{PaO}_2/\text{FiO}_2$  ratio that improved from week 1 to week 2.

Cox proportional hazards regression revealed that smoking, CCI > 6, a lowest week 2  $\text{PaO}_2/\text{FiO}_2$  ratio < 150, and a highest week 2 plateau pressure  $\geq$  30 were univariately associated with 30-day mortality in patients who required PMV (Figure 2). In a multivariate model that included sex, age > 65, smoking, CCI > 6, and the same dichotomous variables for  $\text{PaO}_2/\text{FiO}_2$  ratio and plateau pressure, results were directionally consistent, but all CIs included the null value of 1.0.

## Discussion

Our study demonstrated that PMV is common in patients with COVID-19-related respiratory failure. PMV definition of  $\geq$  21 days of MV is

**Table 1.** Baseline characteristics of COVID-19 patients requiring mechanical ventilation.

Variable	All patients ( <i>n</i> = 355)	Prolonged mechanical ventilation <sup>a</sup> ( <i>n</i> = 86)	Short mechanical ventilation <sup>b</sup> ( <i>n</i> = 269)	<i>p</i> <sup>c</sup>
Demographics				
Age, year, median (IQR)	65 (55, 73)	63 (57, 71)	66 (55, 73)	0.515
Males, <i>n</i> (%)	208 (58.6)	59 (68.6)	149 (55.4)	0.030
BMI, kg/m <sup>2</sup> , median (IQR)	31.3 (26.9, 36.7)	30.2 (26.9, 35.8)	31.5 (26.9, 36.8)	0.675
Race, <i>n</i> (%)				0.639
White	268 (75.5)	62 (72.1)	206 (76.6)	
Black or African American	44 (12.4)	13 (15.1)	31 (11.5)	
Other	43 (12.1)	11 (12.8)	32 (11.9)	
Ethnicity, <i>n</i> (%)				0.005
Hispanic	50 (14.1)	20 (23.3)	30 (11.2)	
Non-Hispanic	305 (85.9)	66 (76.7)	239 (88.8)	
Clinical history, <i>n</i> (%)				
Diabetes	139 (39.2)	34 (39.5)	105 (39.0)	0.934
Coronary artery disease	95 (26.8)	14 (16.3)	81 (30.1)	0.012
Hypertension	228 (64.2)	54 (62.8)	174 (64.7)	0.75
Congestive heart failure	77 (21.7)	7 (8.1)	70 (26.0)	< 0.001
Chronic kidney disease	73 (20.6)	9 (10.5)	64 (23.8)	0.008
Chronic pulmonary disease	62 (17.5)	9 (10.5)	53 (19.7)	0.05
History of cancer	58 (16.3)	10 (11.6)	48 (17.8)	0.175
Liver disease	53 (14.9)	9 (10.5)	44 (16.4)	0.182
Obesity	125 (35.2)	29 (33.7)	96 (35.7)	0.74
Obstructive sleep apnea	79 (22.3)	16 (18.6)	63 (23.4)	0.35
Smoking	144 (40.6)	37 (43.0)	107 (39.8)	0.594
Charlson comorbidity index, median (IQR)	5.0 (3.0, 8.0)	4.0 (3.0, 6.0)	5.0 (3.0, 8.0)	0.027
ICU admission source, <i>n</i> (%)				
Outside hospital	95 (30.1)	31 (37.8)	64 (27.4)	
Hospital ward/Emergency department	210 (66.5)	51 (62.2)	159 (67.9)	
Other	11 (3.5)	0 (0.0)	11 (4.7)	
BMI, body mass index; ICU, intensive care unit; IQR, interquartile range. <sup>a</sup> Mechanical ventilation > 17 days. <sup>b</sup> Mechanical ventilation ≤ 17 days. <sup>c</sup> Between ventilation group comparison by <i>t</i> -test or Wilcoxon's rank sum test (continuous variables), or chi-square or Fisher's exact test (categorical variables).				

**Table 2.** Respiratory parameters, treatments, and outcomes by duration of mechanical ventilation.

Variable	All patients (n = 355)	Prolonged mechanical ventilation <sup>a</sup> (n = 86)	Short mechanical ventilation <sup>b</sup> (n = 269)	p <sup>c</sup>
Respiratory parameters, median (IQR)				
Lowest PaO <sub>2</sub> /FiO <sub>2</sub> ratio				
Week 1	142.0 (116.0, 182.9)	129.0 (115.8, 153.1)	145.0 (116.0, 196.7)	0.017
Week 2	135.0 (98.2, 182.5)	132.5 (110.0, 160.0)	142.5 (78.5, 212.5)	0.946
Highest PCO <sub>2</sub>				
Week 1	57.5 (48.0, 72.0)	67.0 (55.0, 78.0)	55.0 (44.2, 67.5)	< 0.001
Week 2	66.0 (51.0, 76.0)	71.0 (64.5, 82.0)	56.0 (46.2, 71.0)	< 0.001
Highest plateau pressure				
Week 1	29.0 (26.0, 32.0)	30.0 (28.0, 32.8)	29.0 (25.0, 32.0)	0.004
Week 2	30.0 (26.0, 35.0)	32.0 (29.0, 36.0)	28.0 (24.0, 33.0)	< 0.001
Highest driving pressure				
Week 1	18.0 (15.0, 21.0)	18.0 (16.0, 20.0)	18.0 (15.0, 21.0)	0.506
Week 2	19.0 (15.0, 24.0)	21.0 (17.0, 25.0)	18.0 (15.0, 22.0)	< 0.001
Treatments, n (%)				
Prone	244 (68.7)	77 (89.5)	167 (62.1)	< 0.001
Dialysis	61 (17.2)	19 (22.1)	42 (15.6)	0.166
Neuromuscular blockade	227 (66.6)	79 (91.9)	148 (58.0)	< 0.001
Steroids	299 (87.7)	79 (91.9)	220 (86.3)	0.173
Vasopressor	309 (90.6)	83 (96.5)	226 (88.6)	0.03
Tracheostomy	35 (9.9)	34 (39.5)	1 (0.4)	< 0.001
Outcomes				
Mechanical ventilation, days, median (IQR)	9.0 (4.4, 16.7)	24.3 (19.9, 30.1)	7.1 (3.8, 10.8)	< 0.001
ICU LOS, days, median (IQR)	11.4 (5.8, 19.2)	27.3 (21.7, 36.8)	9.1 (4.7, 13.5)	< 0.001
Hospital LOS, days, median (IQR)	17.9 (11.4, 27.4)	31.3 (26.0, 40.2)	14.8 (9.2, 20.3)	< 0.001
30-day mortality, n (%)	156 (43.9)	36 (41.9)	120 (44.6)	0.655
60-day mortality, n (%)	163 (45.9)	40 (46.5)	123 (45.7)	0.899
90-day mortality, n (%)	163 (45.9)	40 (46.5)	123 (45.7)	0.899
Inhospital mortality, n (%)	156 (43.9)	40 (46.5)	116 (43.1)	0.581
Disposition <sup>d</sup>				< 0.001
Rehabilitation facility <sup>e</sup> , n (%)	107 (53.8)	42 (91.3)	65 (42.5)	
Home, n (%)	85 (42.7)	4 (8.7)	81 (52.9)	
Other, n (%)	7 (3.5)	0 (0.0)	7 (4.6)	
ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; PCO <sub>2</sub> , pressure of carbon dioxide.				
<sup>a</sup> Mechanical ventilation > 17 days.				
<sup>b</sup> Mechanical ventilation ≤ 17 days.				
<sup>c</sup> Between ventilation group comparison by <i>t</i> -test or Wilcoxon's rank sum test (continuous variables), or chi-square or Fisher's exact test (categorical variables).				
<sup>d</sup> Among patients surviving to hospital discharge.				
<sup>e</sup> Subacute rehabilitation or skilled nursing facility.				

**Table 3.** Characteristics and outcomes of prolonged mechanical ventilation patients, by 30-day mortality.

Variable	Alive at 30 days (n = 50)	Dead at 30 days (n = 36)	p <sup>a</sup>
Patient characteristics			
Age, year, median (IQR)	63 (53, 68)	66 (59, 75)	0.059
Males, n (%)	30 (60.0)	29 (80.6)	0.043
BMI, kg/m <sup>2</sup> , median (IQR)	31.5 (28.5, 37.4)	28.1 (26.0, 34.1)	0.041
Weight, kg, median (IQR)	94.3 (81.6, 109.6)	91.4 (70.8, 108.5)	0.27
Race, n (%)			0.345
White	38 (76.0)	24 (66.7)	
Black or African American	8 (16.0)	5 (13.9)	
Other	4 (8.0)	7 (19.4)	
Ethnicity, n (%)			0.40
Hispanic	10 (20.0)	10 (27.8)	
Non-Hispanic	40 (80.0)	26 (72.2)	
Smoking, n (%)	16 (32.0)	21 (58.3)	0.015
Charlson comorbidity index, median (IQR)	4.0 (2.2, 5.8)	5.0 (4.0, 6.0)	0.037
Respiratory parameters, median (IQR)			
Lowest PaO <sub>2</sub> /FiO <sub>2</sub> ratio			
Week 1	130.2 (116.4, 155.0)	128.8 (115.6, 147.5)	0.862
Week 2	150.0 (116.0, 172.9)	120.0 (98.3, 152.5)	0.007
Highest PCO <sub>2</sub>			
Week 1	66.5 (58.2, 81.0)	68.0 (53.2, 77.0)	0.992
Week 2	70.0 (64.0, 79.0)	72.0 (65.0, 82.0)	0.762
Highest plateau pressure			
Week 1	30.0 (28.0, 32.8)	30.0 (28.0, 32.2)	0.892
Week 2	31.0 (28.0, 35.0)	34.5 (30.0, 37.0)	0.014
Highest Driving Pressure			
Week 1	17.0 (15.0, 20.8)	18.0 (16.0, 20.0)	0.463
Week 2	20.0 (16.8, 25.0)	22.5 (18.8, 27.0)	0.053
Treatments, n (%)			
Prone	44 (88.0)	33 (91.7)	0.729
Dialysis	10 (20.0)	9 (25.0)	0.581

*(Continued)*

**Table 3.** (Continued)

Variable	Alive at 30 days (n = 50)	Dead at 30 days (n = 36)	p <sup>a</sup>
Neuromuscular blockade	46 (92.0)	33 (91.7)	> 0.999
Steroids	45 (90.0)	34 (94.4)	0.694
Vasopressor	47 (94.0)	36 (100.0)	0.261
Tracheostomy	29 (58.0)	5 (13.9)	< 0.001
Outcomes, median (IQR)			
Mechanical ventilation, days	28.4 (21.1, 37.4)	21.3 (18.4, 25.0)	< 0.001
ICU LOS, days	31.5 (22.8, 39.0)	24.7 (20.5, 27.7)	0.012
Hospital LOS, days,	38.2 (33.0, 45.3)	26.2 (21.1, 28.8)	< 0.001
BMI, body mass index; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; PCO <sub>2</sub> , pressure of carbon dioxide.			
<sup>a</sup> Between ventilation group comparison by <i>t</i> -test or Wilcoxon's rank sum test (continuous variables), or chi-square or Fisher's exact test (categorical variables).			

common but there is substantial variability in the published literature reflecting different patient populations.<sup>17,19,20</sup> In a review of publications on PMV, the cutoff of > 21 days was used only in 28 of 282 studies reviewed.<sup>15</sup> There is no PMV definition specific to COVID-19 patients. A recent publication from an international VIRUS COVID-19 Registry reported median duration of MV of 8.8 days with IQR of 3.3–17 days.<sup>3</sup> The PMV threshold of > 17 days (greater than the 75th percentile of MV duration in the VIRUS COVID-19 Registry) was chosen for this study as the most reflective of the current COVID-19 patient population.

Consistent with studies in other patient populations that have identified higher severity of illness as a predisposing factor for PMV, our PMV patients had more severe respiratory abnormalities during the first 2 weeks of MV than their SMV counterparts.<sup>17,21</sup> The prevalence of comorbidities in our PMV group was lower than in SMV patients, and this difference may be related to earlier care withdrawal, and thus shorter duration of MV, in patients with poor overall prognosis due to advanced comorbid conditions. The higher prevalence of Hispanics in the PMV group requires further investigation in light of previous reports of racial and ethnic disparities in COVID-19 incident rates and outcomes.<sup>22,23</sup>

PMV in non-COVID-19 populations is associated with increased healthcare resource utilization and poorer outcomes, including increased mortality.<sup>24–26</sup> Consistent with this, our study demonstrated an increased need for critical care interventions and specialized post-discharge care as well as longer ICU and hospital LOS in COVID-19 patients with PMV. However, while the overall mortality in our cohort was consistent with earlier publications on ventilated COVID-19 patients,<sup>3,11,27</sup> the absence of a mortality difference between the PMV and SMV groups suggests that a significant number of patients recover following extended periods of MV. A recent report demonstrating successful weaning from MV in the majority of mechanically ventilated COVID-19 patients discharged to long-term acute care facilities supports this observation.<sup>28</sup> However, the more elusive endpoint of post-intensive care syndrome, which often involves impairments in physical, psychiatric, and cognitive domains that affect quality of life and the ability to return to a baseline level of functioning, is common in survivors of COVID-19 related critical illness and requires further investigation.<sup>29</sup>

A comparison of crude mortality in PMV *versus* SMV patients does not account for the complexity of care withdrawal causes in these patients, including advanced comorbidities and/or patient



healthcare directives. A clearer understanding of mortality causes in early *versus* later phases of MV in COVID-19 patients is needed.

To the best of our knowledge, there are no studies to date that have identified predictors of survival in COVID-19 patients requiring extended periods of MV. Factors associated univariately with mortality in our PMV cohort include smoking, CCI > 6, and PaO<sub>2</sub>/FiO<sub>2</sub> ratio < 150 and plateau pressure ≥ 30 during week 2 of MV. These findings are consistent with previously reported associations between higher degree of lung mechanics and gas exchange abnormalities and mortality in acute respiratory distress syndrome patients.<sup>30–35</sup> Multivariate analysis results in the PMV group remained directionally consistent with those from the univariate analysis but did not reach statistical significance due to the relatively small sample size. The lower plateau pressure and higher oxygenation indices in week 2, as well as the week 1 to week 2 improvement in PaO<sub>2</sub>/FiO<sub>2</sub> ratio observed in survivors as compared with non-survivors require confirmation in larger studies. The borderline association of male gender and lower BMI with mortality also requires confirmation. The higher survival rate observed among patients who received tracheostomy likely reflects patient selection bias for the procedure and also requires further investigation.

Study limitations include a retrospective design and the risk of unidentified confounders affecting the outcomes. ECMO patients who commonly require PMV were excluded from the analysis. All three treatment centers used identical treatment guidelines, but differences related to the hospital-specific patient populations could have been present. The number of patients was relatively small, especially in the PMV group, and this limited the strength of the multivariate analyses.

### Conclusion

PMV is common in COVID-19 patients with respiratory failure. Factors associated with the need for PMV include lower PaO<sub>2</sub>/FiO<sub>2</sub> ratio, higher PCO<sub>2</sub> and higher plateau and driving pressures during the first 2 weeks of MV. PMV patients have longer ICU and hospital LOS, require more critical care interventions and have higher needs for post-discharge specialty care. At the same time, the overall mortality in the PMV group and

patients requiring shorter MV is not significantly different. On univariate analysis, factors associated with mortality in PMV patients include smoking, higher CCI, and lower PaO<sub>2</sub>/FiO<sub>2</sub> ratio and higher plateau pressure during week 2 of MV. The results of this study focusing on factors associated with the need for PMV and outcomes in PMV patients with COVID-19 can facilitate clinical decision-making, patient and family counseling, and resource allocation planning.

### Author contributions

**Roman Melamed:** Conceptualization; Investigation; Writing – original draft.

**Francisco Paz:** Investigation; Writing – review & editing.

**Stacy Jepsen:** Investigation; Writing – review & editing.

**Claire Smith:** Data curation; Formal analysis; Writing – review & editing.

**Ramiro Saavedra:** Conceptualization; Writing – review & editing.

**Maximilian Mulder:** Conceptualization; Writing – review & editing.

**Adnan Masood:** Investigation; Writing – review & editing.

**Joshua Huelster:** Investigation; Writing – review & editing.

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**Lori Boland:** Formal analysis; Methodology; Writing – review & editing.

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**Data availability**

The dataset used for this study is available from the corresponding author upon reasonable request.

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