

Hourly Analysis of Mechanical Ventilation Parameters in Critically Ill Adult Covid-19 Patients: Association with Mortality

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Abstract

Objective: There exists controversy about the pathophysiology and lung mechanics of COVID-19 associated acute respiratory distress syndrome (ARDS), because some report severe hypoxemia with preserved respiratory system mechanics, contrasting with “classic” ARDS. We performed a detailed hourly analysis of the characteristics and time course of lung mechanics and biochemical analysis of patients requiring invasive mechanical ventilation (IMV) for COVID-19-associated ARDS, comparing survivors and non-survivors. **Methods:** Retrospective analysis of the data stored in the ICU information system of patients admitted in our hospital ICU that required IMV due to confirmed SARS-CoV-2 pneumonia between March 5th and April 30th, 2020. We compare respiratory system mechanics and gas exchange during the first ten days of IMV, discriminating volume and pressure controlled modes, between ICU survivors and non-survivors. **Results:** 140 patients were included, analyzing 11138 respiratory mechanics recordings. Global mortality was 38.6%. Multivariate analysis showed that age (OR 1.092, 95% (CI 1.014-1.176)) and need of renal replacement therapies (OR 10.15, (95% CI 1.58-65.11)) were associated with higher mortality. Previous use of Angiotensin Converting Enzyme inhibitor (ACEI)/angiotensin-receptor blockers (ARBs) also seemed to show an increased mortality (OR 4.612, (95% CI 1.19-17.84)) although this significance was lost when stratifying by age. Respiratory variables start to diverge significantly between survivors and non-survivors after the 96 to 120 hours (hs) from mechanical ventilation initiation, particularly respiratory system compliance. In non survivors, mechanical power at 24 and 96 hs was higher regardless ventilatory mode. **Conclusions:** In patients admitted for SARS-CoV-2 pneumonia and requiring mechanical ventilation, non survivors have different respiratory system mechanics than survivors in the first 10 days of ICU admission. We propose a checkpoint at 96–120 hs to assess patients improvement or worsening in order to consider escalating to extracorporeal therapies.

Keywords

ARDS, mechanical ventilation, SARS-CoV-2, respiratory system mechanics

Introduction

The clinical spectrum of SARS-CoV-2 infection (COVID-19) ranges from asymptomatic cases all the way to severe disease requiring ICU admission and invasive mechanical ventilation (IMV). The latter is usually characterized by severe community-acquired pneumonia with acute respiratory failure, acute respiratory distress syndrome (ARDS), septic shock and multiorgan failure. Current data suggest that 5–20% of COVID-19 patients develop critical illness.¹⁻³

Controversy exists about the pathophysiology and lung mechanics of COVID-19 associated ARDS, because some report severe hypoxemia with preserved respiratory system mechanics, contrasting with “classic” ARDS^{4,5} that usually associates hypoxemia with a high respiratory system elastance.

A detailed analysis of the characteristics and time course of lung mechanics of patients requiring IMV for COVID-19-associated ARDS and its association with outcome may guide the choice

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of ventilatory strategies. We compared IMV parameters in survivors and non-survivors of Covid-19-related ARDS.

Material and Methods

Our main objective was to compare respiratory system mechanics and gas exchange during the first ten days of IMV between ICU survivors and non-survivors. Secondary objectives were the association of clinical and biochemical characteristics with survival.

We performed a retrospective single-centre observational study. Adult patients admitted to our 46-bed Department of Critical Care at Hospital Clínico San Carlos from March 5 to April 30, 2020 with respiratory failure due to RT-PCR-confirmed SARS-CoV-2 who needed IMV and died or were discharged at the time of study were enrolled. For the study of lung mechanics and gas exchange, only data recorded within the first 10 days of ICU admission were collected (flow chart 1).

Patients were cared for by the usual ICU staff. Due to shortages of ICU ventilators, some patients were ventilated with anesthesia machines.

The Institutional Review Board approved the study and waived the need for informed consent (CEIC 21/170-E).

Clinical and Biochemical Data

All variables were collected retrospectively from the electronic ICU information system (ICCA™ v H.02.01, Philips, The Netherlands). Patient data retrieved were age, sex, ethnicity, race, body mass index (BMI), Apache II score, days from onset of symptoms to ICU admission, ICU length of stay (LOS). Previous history of hypothyroidism, asthma, Chronic Obstructive Pulmonary Disease (COPD), Angiotensin Converting Enzyme inhibitor (ACEI) or angiotensin-receptor blockers (ARBs) and SARS-CoV-2 drug therapy, renal dysfunction and use of renal replacement therapy, as well as extracorporeal membrane oxygenation (ECMO) and ICU mortality were recorded.

ICU admission and daily, hemoglobin, plasma creatinine and urea, lactate and arterial blood gases were registered. The following IMV parameters were recorded every hour: minute ventilation, breath rate, tidal volume, positive end-expiratory pressure (PEEP), peak pressure, driving pressure and respiratory system compliance. Mechanical power and its derived ratios were calculated depending on the ventilation mode. For VC^{6,7}:

$$0.098 \times RR \times TV \times (\text{Peak Inspiratory Pressure} - 0.5 \times \text{driving pressure})$$

For PC^{6,8}:

$$0.098 \cdot RR \cdot TV \cdot (\text{driving pressure} + \text{PEEP})$$

Ventilator ratio (VR) was calculated as previously published by

Sinha et al⁹

$$\frac{\text{measured Minute Ventilation} \times \text{measured PaCO}_2}{\text{predicted Minute Ventilation} \times \text{predicted PaCO}_2}$$

We studied volume control and pressure control recordings separately for each time point separately.

Statistical Analysis

All data were tested for normal distribution with the Kolmogorov–Smirnov test and are presented as mean $\pm$ standard deviation or median with 25th percentile and 75th percentile, as appropriate.

Proportions were compared using χ^2 or Fisher exact tests. For dichotomic variables, T Student test and Mann-Whitney U test were used. Pearson or Spearman correlations were performed for continuous variables. Multivariate logistic analysis was performed using the statistically significant variables of the univariate comparisons between survivors and non survivors. $P < .05$ was considered significant. All analyzes were performed with SPSS v.25 (IBM Inc., USA).

Results

154 RT-PCR-confirmed Covid-19 patients were admitted during the study period, of whom 14 remained in the ICU at the time of analysis and were excluded.

Admission and baselines characteristics of survivors and non-survivors are listed in Table 1. All patients required mechanical ventilation and the global mortality was 38.6%. Significant differences between survivors and non survivors were observed in Apache II score, age, prior ACEI/ARB therapy, need for vasopressors, use of ECMO and renal dysfunction.

Multivariate analysis showed that age, previous use of ACEI/ARBs and need of renal replacement therapies were associated with higher mortality (Table 2).

Invasive Mechanical Ventilation Parameters During the First 10 Days

We collected a total of 19 545 recordings and excluded 8407 not associated with pressure or volume controlled ventilator modes, leaving 11 138 recordings for analysis (Figure 1).

In the first 5 days pressure control (PC) was the most frequently used ventilation mode, followed by volume control. Beyond this time point, patients were increasingly ventilated in pressure support (PS) mode (Figure 2). There was no difference in the use of prone positioning in the first 24 hs of admission.

A significant difference between survivors and non-survivors were observed for PaO₂/FiO₂ ratio (Figure 3b) and ventilatory ratio (Figure 3a). Lung mechanics were similar over the first 96–120 hours but started to show significant differences beyond these time points. Significantly higher levels of PEEP were used in survivors from the start of mechanical ventilation (Figure 4).

Table 1. Demographics and Baseline Characteristics.

	Survivors, n = 86	Non Survivors, N = 54	P
Age, median (SD)	57 (51-66)	66 (57.75-73)	<.001
Male sex, n (%)	55 (64)	38 (70.4)	.276
Hispanic/latino ethnicity, n (%)	23 (26.7)	17 (31.5)	.338
Comorbidities			
Hypothyroidism n (%)	11 (12.8)	7 (13)	.585
ACE inhibitors or ARBs, n (%)	25 (29.1)	25 (46.3)	.03
Asthma, n (%)	7 (8.1)	4 (7.4)	.574
COPD, n (%)	9 (10.5)	6 (11.1)	.557
Median, interquartile range			
BMI,	27.7 (25.7-31.2)	27.55 (25.9-29.4)	.556
Apache II	14 (9-19)	20 (15.5-26.5)	<.001
Admission to ICU, days	1 (0-5)	1.5 (0-5.25)	.812
Onset of symptoms, days	10 (6.75-12.25)	8 (7-12)	.516
ICU LOS	14 (8-24.5)	16.5 (8.75-24.25)	.988
Plasma creatinine, mg/dl	0.78 (0.62-0.99)	0.83 (0.65-1.3)	.166
Plasma urea, mg/dl	50.5 (34.75-70.25)	53 (37.5-70.75)	.285
Drug therapy			
Lopinavir/ritonavir, n (%)	66 (76.7)	40 (74.1)	.435
Hydroxychloroquine, n (%)	84 (97.7)	52 (96.3)	.501
Interferon beta, n (%)	33 (38.4)	18 (33.3)	.338
Tocilizumab, n (%)	41 (47.7)	20 (37)	.144
Corticosteroids, n (%)	57 (66.3)	38 (70.4)	.377
Acetylcysteine, n (%)	28 (32.6)	10 (18.5)	.051
Ceftriaxone, n (%)	77 (89.5)	52 (96.3)	.129
Azithromycin, n (%)	57 (66.3)	31 (57.4)	.190
Noradrenalin, n (%)	57 (66.3)	45 (83.3)	.020
Outcomes			
Oliguria, n (%)	18 (20.9)	19 (35.8)	.042
Renal replacement therapy, n (%)	4 (4.7)	13 (24.5)	.001
Prone position first 24 hs, n (%)	22 (25.9)	15 (28.3)	.452
ECMO, n (%)	0	4 (7.4)	.021

Abbreviations: ACE, angiotensin-converting-enzyme; ARBs, angiotensin-receptor blockers; COPD, chronic obstructive pulmonary disease; BMI, body mass index; LOS, length of stay; MRSA, Methicillin-resistant *Staphylococcus aureus*.

In bold: $P < .05$.

Table 2. Multivariate Analysis for Mortality.

Variable	Odds Ratio	P Value
Age	1.092 (1.014-1.176)	.021*
APACHE II	1.099 (0.99-1.22)	.073
ACE inhibitors	4.612 (1.19-17.84)	.027*
Oliguria	0.253 (0.05-1.2)	.084
RRT	10.15 (1.58-65.11)	.015*
Noradrenaline	1.3 (0.33-5.07)	.7
ECMO	—	.99

* $p < 0.05$

Characteristics at 1, 24 and 96 hours of Invasive Mechanical Ventilation

In the first hour of IMV, survivors had a significantly lower plasma lactate levels, whereas all other parameters were similar.

At 24 hours of IMV, results are different according to ventilation modes. In VC mode, non-survivors had a significantly lower $\text{PaO}_2/\text{FiO}_2$ ratio and higher VR than survivors. However, driving pressure and respiratory system compliance were not different.

Mechanical power and its normalized ratios (for IBW and Crs) were higher in non-survivors, who were ventilated with lower PEEP values, higher respiratory rates (RR) and higher tidal volumes (TV). In PC mode, gas exchange variables were also different. Respiratory system compliance was lower in non-survivors. Mechanical power was higher in non-survivors who were ventilated with higher driving pressure and RR.

At 96 hours of IMV, we found that non-survivors ventilated in VC or PC mode, had significantly higher hemoglobin and lactate levels and higher ventilatory ratio. Mechanical power was higher in non survivors, regardless off ventilatory mode. $\text{PaO}_2/\text{FiO}_2$ ratio was not different in VC mode, but lower in PC. Non-survivors in VC mode were also ventilated with higher RR and driving pressures but lower PEEP levels and their respiratory system compliance was lower. In PC mode, tidal volume, PEEP and driving pressure were not different but minute ventilation and RR were higher.

Discussion

To the best of our knowledge, this is the first observational study describing the course of mechanical lung parameters of

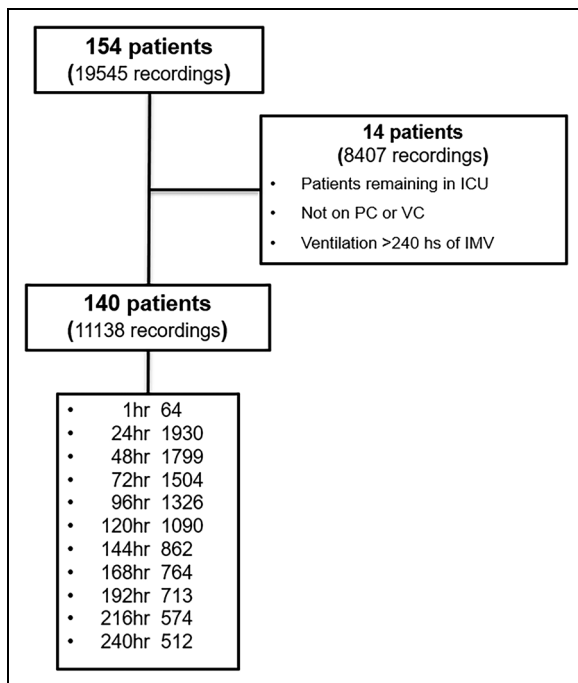


Figure 1. Flow chart of all the recordings from the mechanical ventilation included in the analysis. PC: Pressure-Controlled ventilation; VC: Volume-Controlled ventilation; IMV: Invasive Mechanical Ventilation.

critically ill Covid-19 patients during IMV and their association with mortality, using a high-resolution analysis based on hourly recordings.

Earlier studies report mortality rates in mechanically ventilated Covid-19 patients as high as 60%.¹⁰⁻¹² Mortality in our cohort was like more recent non-Covid-19 ARDS series (Bellani et al¹³), and characterized by non-survivors being predominantly male, older ($P < .001$) and with higher mean APACHE II score ($P < .001$). Interestingly, body mass index in our series was not associated with a higher mortality ($P = .556$), although height and weight are only estimated in our patients and bias cannot be excluded.

ACEI/ARBs treatment was associated with increased mortality ($P = .03$), a finding in sharp contrast with the results of other studies.^{14,15} However, this association is no longer significant when adjusting for age. We found that elderly patients were more frequently receiving ACEI/ARBs treatment before admission (see Figures E1 and E2 in the Online Data Supplement).

Renal function at admission was similar in both groups, but patients requiring renal replacement treatment (RRT), delivered by continuous veno-venous haemodialysis or haemodiafiltration had a significantly higher risk of dying in the ICU using the multivariate analysis ($P = .015$). Although, SARS-Cov-2 may cause direct kidneys injury (Su et al¹⁶), IMV may contribute indirectly by influencing systemic hemodynamics. We found that controlled IMV on day 6 (144 hs) was associated with renal failure, an association previously reported by Hirsch et al¹⁷ on day 8 of ICU admission.

Serum lactate dehydrogenase (LDH) increased in the first 24 hours of IMV and remained elevated during the first 10 days. We found a negative correlation between LDH increase and dynamic compliance in survivors at all time points. This correlation was positive in non survivors, although not significant. Correlations of LDH serum concentrations with oxygenation and ventilation variables were significant ($P < .05$) (Table 3). We hypothesize that LDH elevation reflects increasing lung inflammation rather than VILI. We did not measure LDH isoenzymes, particularly type 3, which were related to acute lung injury in previous studies.^{18,19}

Respiratory variables (gasometric, such as VR, and mechanical, i.e mechanical power, dynamic compliance, PEEP) start to diverge significantly between survivors and non-survivors during the 96 to 120 hours time interval ($P < .05$) (Figures 2 and 3 and Table E1). IMV variables and blood gases showed significant differences when IMV is switched from controlled to assisted modes (Figure 3), and this seems to be associated with a higher mechanical power and TV applied in non-survivors, as well as a significantly higher respiratory rate and driving pressure at both time points. In all patients we titrated PEEP using a dynamic compliance-guided protocol. Because non-survivors had a lower recruitability, they were ventilated with lower PEEP values.

The significant association of a higher mechanical power and mortality merits further study as a potentially modifiable factor of IMV settings in Covid-19-associated ARDS. TV at 96 hours were not different ($P = .22$) and VT/IBW remained always below 8 ml/kg²⁰ although this may not be as relevant as they are in “classic” ARDS.^{4,5} However, respiratory rate was clearly higher in non-survivors ($P < .001$). Interestingly, we found that respiratory mechanics in VC mode were also significantly different in non-survivors ($P < .001$). Therefore, considering the MP equation,⁷ in VC, the only modifiable variable is respiratory rate. Accordingly, PEEP was titrated using a dynamic compliance-guided protocol and TV/IBW was within accepted limits, although lower TV of 6 ml/kg could have been set.²⁰ Respiratory system compliance, a surrogate of elastance, was lower during VC starting with ICU admission and can therefore not be attributed to mechanical ventilation settings, as mentioned above. We, therefore, consider that the choice of ventilation mode was rather related to attempts to optimize gas exchange and minute ventilation in patients with more severe disease, although higher RRs and driving pressures at 24 hs might have favored the development of VILI in our patients. The consequence of these ventilator settings might be the rise of driving pressures and the decrease of respiratory system compliance at 96 hs. Cressoni et al observed that even a short (less than 24 h) course of high-energy ventilation induces VILI,²¹ a finding that correlates with our results.

Finally, 96–120 hours parameters may be used as a “check-point” to assess whether a patient it is improving or deteriorating and consider intensifying protective ventilation with extracorporeal support techniques. The Extracorporeal Life Support Organization Covid-19 guidelines contraindicate

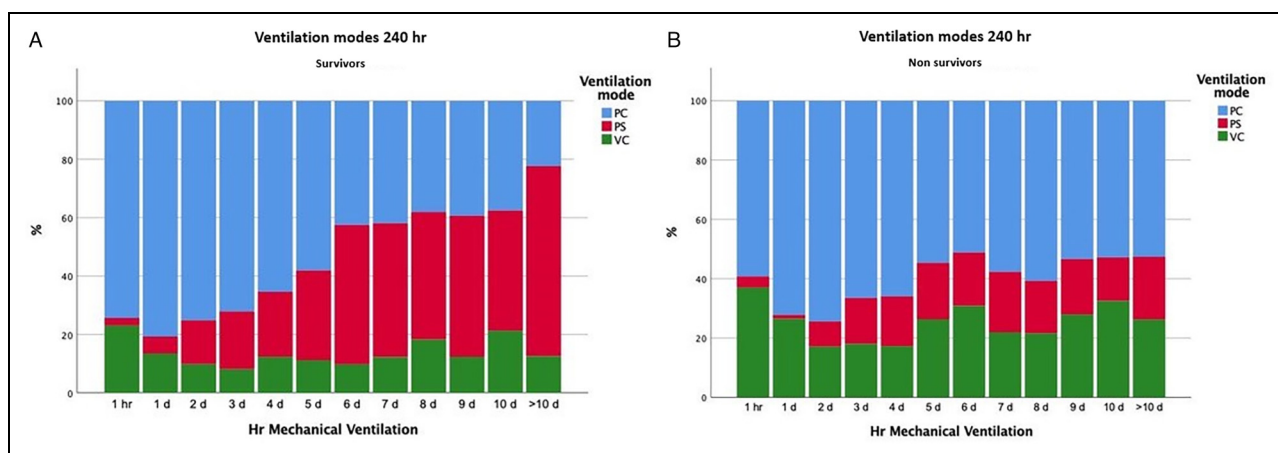


Figure 2. Percentage prevalence of ventilation modes in survivors (A) and non-survivors (B) over the first 10 days of mechanical ventilation. Hr: hours. PC: Pressure-Controlled ventilation. PS: Pressure-Support ventilation. VC: Volume-Controlled ventilation.

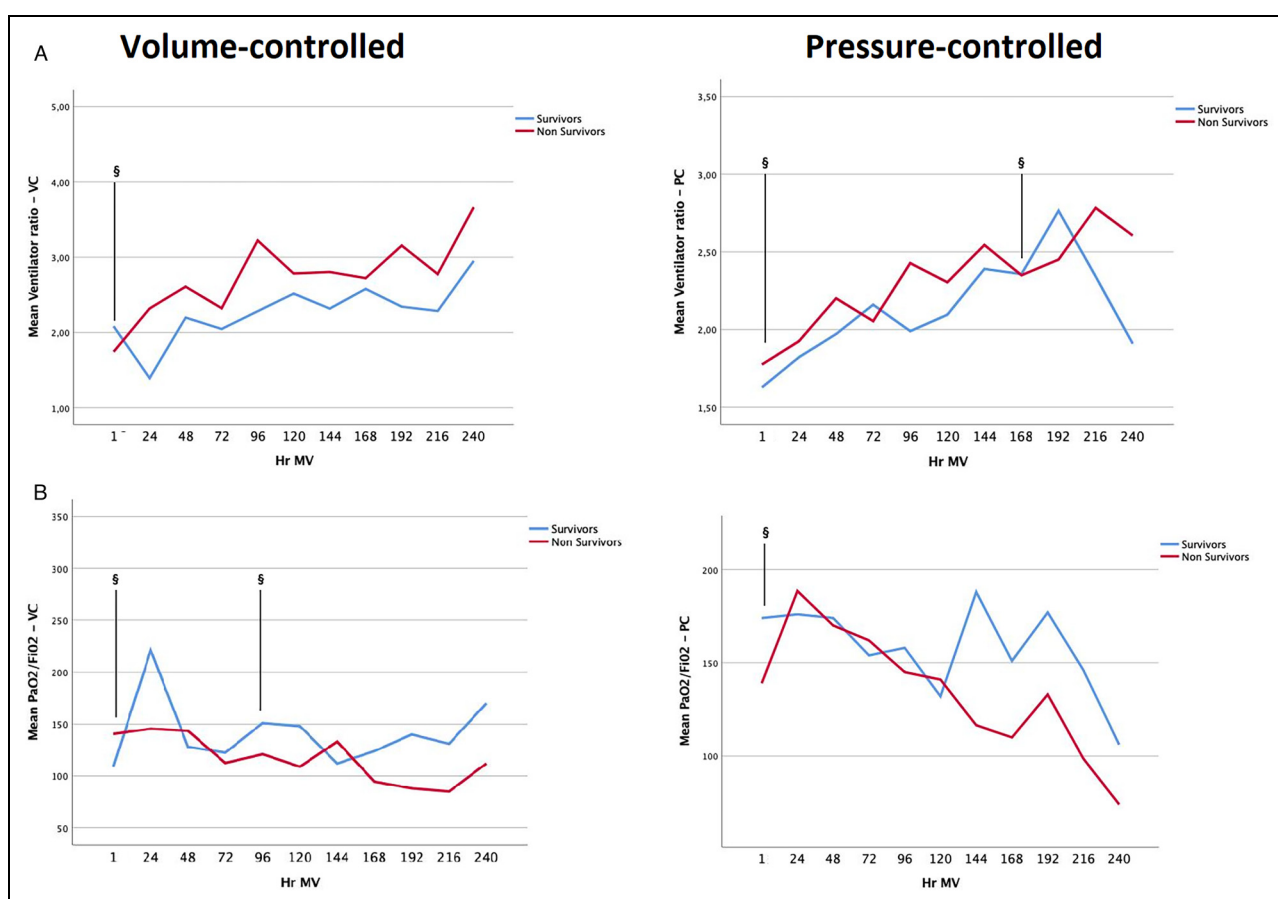


Figure 3. Median ventilatory ratio (A) and PaO₂/FiO₂ ratio (B). Hours of mechanical ventilation plotted on x-axis over the first 10 days in survivors and non-survivors and in volume and pressure-controlled modes (VC and PC respectively). Non statistically significant differences between variables are represented by §; all other values have a statistical significance with $P < .05$.

ECMO for patients mechanically ventilated for more than 10 days²² and in most centers longer than 7 days. Recently published studies about the use of ECMO in Covid-19 patients report a median of 4 days between intubation and ECMO initiation.²³⁻²⁵ Our results suggest that less restrictive time window

may be preferable. Specifically, worsening respiratory mechanics and not oxygenation should be considered to be an early indication of ECMO, because they occur earlier, and prevention of VILI seems to be the most relevant objective in Covid-19 patients.

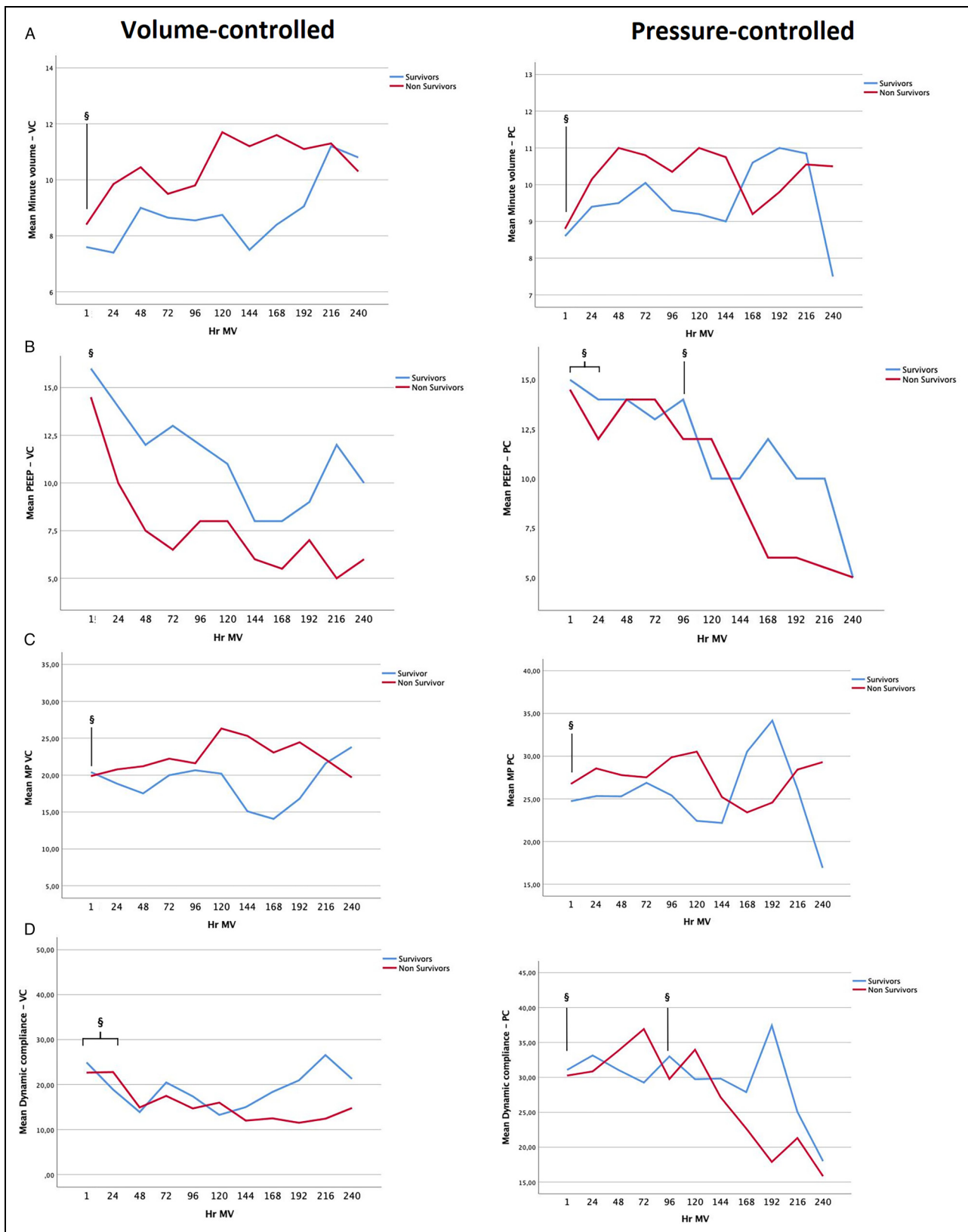


Figure 4. Mean minute volume (A), PEEP (B), mechanical power (C) and dynamic compliance (D). Hours of mechanical ventilation plotted on x-axis by hours of mechanical ventilation over the first 10 days in survivors and non-survivors in volume and pressure-controlled ventilation modes. Non statistically significant differences between variables are represented by §; all other values have a statistical significance with $P < .05$.

Table 3. Correlations between LDH and Dynamic Compliance, PaO₂/FiO₂ and Ventilator Ratio. Spearman bivariate correlation. *P < .05.

Hours of IMV		Cdyn	pO ₂ /FiO ₂	Ventilator Ratio	MP	
					VC	PC
24	Survivors	-0.197*	-0.190*	0.206*	0.022	0.240*
	Non-Survivors	0.041	0.171*	0.271*	0.161*	0.335*
96	Survivors	-0.366*	-0.308*	-0.086*	0.058	0.072
	Non-Survivors	0.172*	0.095*	0.095*	0.758*	0.266*
>144	Survivors	-0.466*	-0.181*	-0.234*	-0.105*	-0.283*
	Non-Survivors	0.017	-0.52*	0.237*	0.349*	0.173*

Limitations to This Study

We acknowledge limitations of our single-center study. ICU ventilator shortage required the use of anesthesia machine ventilators. This may have resulted in differences in ventilator settings and patient care in general not captured by our data collection and thus influenced our results. Our analyzes also did not include other factors associated with different ventilator modes, like the characteristics of administration of sedatives and neuromuscular blockers. Due to the retrospective nature of our study, assessment of regional lung perfusion or shunt fraction, which would help explain the differences in oxygenation and ventilation variables, were not available.

Conclusions

We describe the clinical course over the first 10 days of IMV in Covid-19 patients and the variables associated with mortality. RR might be a modifiable cause for VILI in these patients. Future studies are needed to evaluate whether modification of ventilation strategies or the use extracorporeal supportive interventions, particularly in the first 5 days from admission in the ICU, have an impact on prognosis.

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Author Contributions

TFG, ANR and MSG designed the study. TFF, ANR and JL extracted and analyzed the data. TFF, JL, MCR, VYZ and SDM drafted the article. MSG revised the article and supervised the project. All authors revised the manuscript.

Declaration of Conflicting Interests

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Ethical Approval

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Supplemental Material

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