Intubation Timing as Determinant of Outcome in Patients with Acute Respiratory Distress Syndrome by SARS-CoV-2 Infection

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Research

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Abstract

Background: SARS-CoV-2 infection presents in many cases with pneumonia and respiratory failure. It is not clear whether the time of intubation and connection to mechanical ventilation (MV) in this condition is associated with an increase in mortality or represents the natural course of the disease.

We conducted an observational, prospective, single-center study to describe the characteristics and outcomes of acute respiratory distress syndrome (ARDS) patients with confirmed COVID-19 and treated with invasive MV to determine whether the time-to-intubation following hospital admission is associated with worse outcomes.

Methods: We prospectively included consecutive patients with SARS-CoV-2 infection and moderate to severe ARDS, admitted to an intensive care unit (ICU) and connected to MV between March 17 and July 31, 2020. We examined their general characteristics, ventilatory management, and clinical outcomes. Time of intubation was defined as the time from hospital admission to endotracheal intubation and was categorized as early (<72 hours) or late (≥72 hours). Mann-Whitney U, Kruskal Wallis, chi-square, and Fisher's exact, were used when appropriate. Uni and multivariate analyses between main outcome and explanatory variables were performed.

Results: A total of 183 consecutive patients were included, 28% (51/183) were female, and their median age was 62 years [54-70]. One hundred (55%) patients were subjected to early and 83 (45%) to late intubation. Patients intubated after 72 hours were older and presented more comorbidities. Mortality was higher in the group of patients with late intubation (41% versus 21%; p= 0.002), a PaO_2/FiO_2 ratio <100 mmHg at admission (p= 0.029), and that were older than 60 years (p= 0.008).

Conclusions

In acute COVID-19 patients with moderate to severe ARDS, intubation after 72 hours following hospital admission, age >60 years-old and a PaO_2/FiO_2 ratio <100 at admission may appear to be associated with increased ICU mortality. Further studies are required to confirm our findings and establish the best timing for intubation in COVID-19 patients admitted to the ICU with respiratory failure.

Background

Pneumonia associated to SARS-CoV-2 (COVID-19) may evolve to acute respiratory distress syndrome (ARDS), which is associated with a high mortality risk (1)(2)(3)(4). Many patients are admitted with pneumonia and arterial hypoxemia without evidence of dyspnea, increased work of breathing or impending fatigue(5)(6)(7). Long-accepted clinical practice and expert consensus support prompt intubation of patients with severe hypoxemia (8)(9). However, due to the high demand for intensive care unit (ICU) beds during the pandemic (6), some authors have advocated for a conservative approach, promoting high-flow nasal cannula (HFNC) (10), or non-invasive ventilation (11) while the patient is in an awake prone position (12)(11)(10).

Apart from the well-known risks of mechanical ventilation (MV), as infection (13) and ventilator-induced lung injury (14)(15), among others, potential shortage of ICU resources related to massive demand for MV during the pandemic has added stress and uncertainties to clinicians managing these acute patients (16). Furthermore, many of these patients exhibited a highly unstable condition, worsening after an initial improvement and eventually required intubation. It is not clear whether time-to-intubation directly associates with increased mortality in COVID-19 hypoxemic patients (17).

A recent study showed that neither time from ICU admission to intubation nor HFNC use were associated with increased mortality (18) in a time frame of 8 hours. However, different criteria may influence the moment of admission to the ICU, ranging from the initial clinical impression despite poor oxygenation, to bed-availability. Unlike ICU admission, hospital admission is objectively based on hypoxemia with diverse manifestations of dyspnea or increased work of breathing (WOB) in COVID-19 patients.

Our main objective was to determine whether the time-to-intubation in COVID-19 patients following hospital admission is associated with outcomes. To address this issue, we analyzed a prospectively collected database of mechanically ventilated COVID-19 patients treated in our ICU during the peak months of the pandemic.

Materials And Methods

This prospective observational study was carried out at the Clinical Hospital of the UC-CHRISTUS Health Network, in Santiago, Chile. Patients with laboratory confirmed SARS-CoV-2 infection and moderate to severe ARDS (19), were consecutively included between March 17 and July 31, 2020. Admission pathways comprised the emergency department, and basic ward.

The Institutional Ethics Committee approved this project (Research Ethics Committee Nº 200504004, Faculty of Medicine, Pontificia Universidad Católica de Chile), and waived the need for informed consent.

Laboratory confirmation of SARS-CoV-2 was defined as a positive real-time reverse transcriptase polymerase chain reaction (RT-PCR) result of nasal and pharyngeal swabs.

Our university hospital has a 32-bed both medical-and-surgical ICU with extracorporeal membrane oxygenation (ECMO) capability. Due to the COVID-19 pandemic, the hospital ICU capacity was surged incorporating up to 56 beds from other reconverted units, as needed.

Intensivists and ICU-trained nurses were deployed to these expanded ICUs to ensure a similar standard of care.

All patients undergo an initial respiratory failure management protocol that includes HFNC and the awake prone positioning if tolerated. Orotracheal intubation and connection to MV was performed if the patient had an increased WOB (tachypnea > 30 / min and the use of accessory muscles, paradoxical breathing, altered consciousness, or an hyperadrenergic state), refractory hypoxemia (O2 saturation < 90% despite prone position and HFNC at maximum fraction of inspired oxygen (FiO2) or the presence of concomitant

shock (Additional file 1). The decision to intubate was by attending physicians, and MV started in the volume-control ventilation mode according to local management protocol (Additional file 1).

Data Collection

Data were recorded prospectively by the research team in an electronic worksheet. The study data were recorded prospectively by the research team during the patient's stay in the ICU and collected and managed using the REDCap electronic data capture tools hosted at Pontificia Universidad Católica de Chile.

Clinical data included sex, age, weight, height, medical comorbidities, days since the start of symptoms, laboratory parameters, and PaO_2/FiO_2 ratio by the time of hospital admission. The Acute Physiology and Chronic Health Evaluation (APACHE) (20) and Sequential Organ Failure Assessment (SOFA) scores(21) were calculated within 24 hours of ICU admission. Subsequently, clinical, laboratory and ventilatory parameters were recorded both on day 1 from the start of invasive MV and included: respiratory support mode, positive end-expiratory pressure (PEEP) level, arterial blood gases and F_IO_2, and respiratory system compliance (Crs).

Outcomes

Time of intubation was defined as the time from hospital admission to endotracheal intubation, and classified as lower than 72 hours (early) and equal or higher than 72 hours (late), according to published data (17) and authors consensus. The primary outcome was in-hospital death after receiving MV. Secondary outcomes included duration of MV, ICU and hospital length of stay, and mortality on day 28 and on discharge from the ICU.

Statistical Analysis

For variables with non-normal distribution, non-parametric tests were used. Accordingly, descriptive statistics are shown as medians [interquartile range 25–75] or percentages (%). Mann-Whitney U, Kruskal Wallis, chi-square, and Fisher's exact, were used when appropriate. We performed univariate analyses between main outcome and clinical and laboratory variables. Those with a univariate p-value of 0.1 were included in the multivariate analysis plus other clinically relevant ones. Logistic models were fitted testing individual and interaction variables. Multivariable fractional polynomial methods were also used in order to preserve the continuous nature of important covariates as PaO_2/FiO_2 ratio, time to intubation and age, since we did suspect that their relationships with other variables were non-linear.

As mentioned, for hypoxemia and intubation times we used published cutoffs (17).

We did not use APACHE II for fitting multivariate models to avoid overadjustment, since age was incorporated as an individual variable or in the CALL score, PaO_2/FiO_2 ratio was a relevant individual variation, and comorbidities were represented in the regression models, as well.

Data was analyzed using Graphpad Prism 7 (Graphpad Softwares, La Joya, CA), and Stata 16 (StataCorp, College Station, TX. USA) statistical packages. Two-tailed p value of < 0.05 was considered as statistically significant.

Results

During the study period, 1233 patients with confirmed COVID-19 were admitted, of which 350 evolved with PaO_2/FiO_2 ratio < 200 mmHg. Of these, 25 (7.1%) patients, underwent a limitation on life-support techniques. Fifty-nine (16.9%) patients were intubated upon admission to the ICU, while 266 (76%) underwent a HFNC and/or prone trial, of which 142 (53.4%) patients did not require MV during hospitalization. Thus, 183 patients with confirmed COVID-19 required invasive ventilatory support and were included in the study (Fig. 1)

Demographic and clinical characteristics of patients are shown in Table 1. Overall, 132 patients (78%) were men, their median age was 62 years (54–70), and 138 patients (75%) had one or more comorbidities being hypertension (48%), diabetes (33%) and other cardiovascular diseases (8.2%) the most common.

Table 1
Clinical characteristics, severity scoring and relevant outcomes of patients with severe COVID-19 respiratory failure according to timing from admission to orotracheal intubation.

	All	< 72 hours to OI	> 72 hours to OI	P-value
Number	183	100	83	
Age (years)	62 [54–70]	60 [52–68]	64 [55–71]	0.04
Female (%)	51/183 (28%)	29/100 (29%)	21/83 (25%)	0.6
Comorbidities				
Diabetes Mellitus (%)	61/183 (33%)	29% (29/100)	47% (32/83)	0.01
Hypertension (%)	87/183 (48%)	48/100 (48%)	39/83 (47%)	0.9
BMI (kg/m2)	29 [27–32]	30 [28–33]	28 [26–31]	0.007
APACHE score	12 [8–17] (139)	12 [8–16]	13 [8–20]	0.5
SOFA score	5 [3–8] (139)	5 [3–8]	5 [2–8]	0.4
CALL Score	11 [9–12]	10 [8–12]	11 [10–12]	0.02
Laboratory values				
Ferritin (ng/mL)	1449 [809–2168]	1449 [809–2168]	1450 [1002–2359]	0.8
D-Dimer (ng/mL)	2408 [1078–5538]	2265 [1052–5523]	1858 [1082–4749]	0.6
Lymphocytes, (10e3/µL)	0.63 [0.43–1.02]	0.7 [0.5–1.1]	0.59 [0.43–0.9]	0.03
PaO2/FiO2 at ICU admission	110 [78–164]	123 [84–166]	94 [76–154]	0.052
Categorical variables are expressed as frequency and percentage (%), and continuous variables as median and interquartile range 25,75 [IQR]				
Abbreviations: BMI Body Mass Index, COPD chronic obstructive pulmonary disease, APACHE II Acute Physiology and Chronic Health Evaluation II, SOFA sequential organ failure assessment				

Multivariate analysis

Multivariate logistic regression showed that PaO_2/FiO_2 ratio at admission (OR 0.97 [0.94–0.99], p = 0.016), time to intubation (OR 1.01 [1.00–1.00], p = 0.013), age (OR 1.09 [1.04–1.14], p = 0.001), and angiotensin converting enzyme inhibitors (ACE) inhibitors use (OR 9.91 [2.15–45.7], p = 0.03) were significantly associated with mortality. Other variables tested in the same model (D-dimer (p = 0.296), LDH (p = 0.822), and lymphocytes count at admission (p = 0.644)) did not reach statistical significance. However, the recent developed CALL score, which incorporated PaO_2/FiO_2 ratio, LDH, age, lymphocytes

count, and comorbidities, reached statistical significance in a multivariate model (OR 1.39 [1.06–1.82], p = 0.018), as well as the D-dimer (OR 1.00 [1.00–1.00], p = 0.031).

We explored if number of days before hospital admission associated with outcome, but this variable did not show statistical significance, both as an individual one or as a part of an interaction term alongside with other variables, including time-to-intubation.

In another multivariate logistic regression, the PaO_2/FiO_2 ratio test < 100 mmHg and late intubation as an interaction term were significantly associated with mortality in the ICU, with higher mortality in the group with PaO_2/FiO_2 ratio < 100 with late intubation (Fig. 2). In addition, patients with late intubation exhibited lower compliance and driving pressure on the first MV day compared to the early intubated group, while PaO_2/FiO_2 ratio, and height-adjusted tidal volume were similar (Table 2).

Table 2
Mechanical ventilation variables according to study group at day 1

	All Ventilated Patients			PaO2/FiO2 < 100 mmHg		
	< 72	> 72	P-value	< 72	> 72	P-value
Respiratory Rate	26 [24–28]	26 [24–30]	0.4	26 [23–30]	28 [24–30]	0.6
Tidal Volume (ml)	400 [351—430]	380 [320–400]	0.1	380 [342—400]	354 [307–400]	0.1
Tidal Volume/ Ideal Body Weight (ml/kg)	6.2 [5.8–6.8]	5.9 [5-6.5]	0.2	5.9 [5.7–6.3]	5.6 [5-6.2]	0.2
PEEP (cmH20)	10 [8–10]	8 [6–10]	0.01	10 [8–12]	8 [6–10]	0.02
P Plateau (cmH20)	20 [19–23]	21 [19–24]	0.4	21 [18–24]	22 [20–24]	0.3
Crs (ml/cmH20)	33 [39–40]	32 [22–38]	0.06	32 [30–39]	25 [20–34]	0.01
Driving Pressure (cmH20)	11 [10–13]	12 [10–15]	0.08	12 [9–13]	13[11–17]	0.02
PaO_2/FiO_2 ratio (mmHg)	163 [124–200]	130 [107–170]	0.01	132 [89–173]	120 [96–143]	0.5
pH	7.34 [7.28–7.40]	7.33 [7.26–7.4]	0.7	7.37 [7.28–7.43]	7.36 [7.26–7.4]	0.7
PaCO2 (mmHg)	45 [38–51]	48 [42–58]	0.02	49 [38–54]	47 [41–61]	0.4
Categorical variables are expressed as frequency and percentage (%), and continuous variables as median and interquartile range 25,75 [IQR]						
Abbreviations: PEEP positive end-expiratory pressure; Crs respiratory system compliance						

Table 3
Outcomes by time from ICU admission to intubation.

	All	< 72 hours to OI	> 72 hours to OI	P-value
		Nº 100	Nº 83	
28-day Mortality (%)	39 (21%)	14 (14%)	25 (30%)	0.008
ICU Mortality (%)	56 (31%)	21 (21%)	35 (41%)	0.002
HFNC pre-OI (%)	109 (60%)	38 (37%)	71 (88%)	0.001
Prone position (%)	130 (71%)	71 (71%)	59 (71%)	0.99
Tracheostomy (%)	45 (25%)	21 (21%)	24 (29%)	0.22
MV Days (days)	14 [8–29]	13 [8–25]	17 [9–33]	0.23
Ventilator-free days (days)	14 [0–20]	15 [3–20]	12 [0–20]	0.28
RRT (%)	24 (13%)	13 (13%)	11 (13%)	0.96
ICU LOS (days)	18 [9–33]	15 [9–27]	23 [12–37]	0.01
Hospital LOS (days)	32 [21–52]	31 [18–48]	36 [24–56]	0.02
Categorical variables are expressed as frequency and percentage (%), and continuous variables as median and interquartile range 25,75 [IQR]				
Abbreviations: ICU, Intensive care unit; HFNC: high-flow nasal cannula; OI: orotracheal intubation; MV: Mechanical ventilation; RRT: renal replacement therapy; LOS: length of stay				

Time-to-intubation was also associated with significant differences on early arterial pCO2, arterial pH, tidal volume and pulmonary Crs (Additional file 2).

Discussion

Our main finding is that among hospitalized patients with COVID-19 and requiring MV, intubation after 72 hours of hospital admission and PaO_2/FiO_2 ratio on admission < 100 mmHg was associated with increased mortality. In addition, age > 60 years-old, and previous use of ACE inhibitors were also associated with increased mortality.

The timing of intubation in patients with COVID-19 has been the subject of intense debate. While some advocate for early intubation, others claim for a more conservative approach, trying noninvasive methods (NIV, HFNC and prone) (22) to prevent intubation an connection to MV (23). In our patients, the decision to intubate was based on clinical judgment and may express different clinical tracks of these patients (24). Some were admitted with overt respiratory failure, others progressed steadily to respiratory failure, while others deteriorated after an initial period of improvement.

Furthermore, patients intubated after 72 hours and with a PaO2 / FiO2 ratio < 100 mmHg exhibited lower pulmonary Crs, lower pH, and higher pCO2 after intubation. Clearly, these patients were sicker and developed a progression of their disease. However, we cannot establish the true reason for this progression, which could be explained by the natural evolution of the disease or it could be a phenotype with a specific progression trajectory, but which is also not explained by what was described at the beginning of the pandemic (25). Another probable cause could be given by the spontaneous unregulated ventilatory effort for prolonged periods of time and that would be capable of inducing the progression of lung damage, what we currently known as patient self-inflicted lung injury (P-SILI) (26)(27). Considering that the current knowledge on the role of P-SILI in the progression of lung disease is very limited and there are many aspects of it that are still under debate (22), this would not provide justification for liberal use of endotracheal intubation (22)(28).

Our findings differ from the results reported by a recent study addressing the impact of the time from ICU admission to intubation on outcome (18). In this study the median from hospital to ICU admission was 1.0 days. In consequence, in this short time frame an intubation at 8 or 24 hours did not produce a significant difference in outcome. We can speculate that the small period of time between hospital admission to ICU admission could have effectively limited the damage an eventual P-SILI could provoke after a longer time of spontaneous or assisted ventilation in hypoxemic COVID-19 patients.

Almost half of the total number of patients with PaO_2/FiO_2 ratio < 200 mmHg admitted to our center did not require MV. Most of them underwent a trial of awake prone and/or HFNC for the management of respiratory failure. These findings confirmed that the use of awake prone and/or HFNC may be useful in COVID-19 patients with respiratory failure as have been published (29)(12)(10). Although it is true, patient with PAFI < 100 at admission and who were intubated after 72 hours, a prone and HFNC trial could help a significant number of patients avoid intubation and its potential complications without an increase in mortality (29), especially in a pandemic situation.

Our study has several limitations. First, it is a single center cohort study, in a tertiary academic hospital, not reflecting necessarily the reality of other hospitals in our country, in which prioritization and triage of MV was even more demanding. Second, we followed a ventilatory management protocol that included HFNC trial, awake proning position, prolonged proning cycles, and ultra-protective ventilation, among other interventions. Notwithstanding that this protocol has physiological and clinical rationale, and is evidence-supported, it could differ from other centers' algorithms, hindering the external validity of our results. Finally, as we previously mentioned, our results are only hypothesis generating, but provide mounting evidence to guide future decision-making and promote further clinical research.

Conclusion

In conclusion, we found that hospitalized patients with COVID-19 admitted with PaO2 / FiO2 < 100 mmHg and intubated 72 hours after hospital admission had an increase in mortality. Other identifiable risk factors on admission, such as age > 60 years and the use of ACE inhibitors, may increase the risk

associated with late intubation. Further studies are required to confirm our findings and establish the best time for intubation in COVID-19 patients admitted with moderate to severe ARDS, as well as a more appropriate ventilatory approach and support.

Abbreviations

ARDS, Acute respiratory distress syndrome.

ICU, Intensive care unit.

WOB, work of breathing.

HFNC, high-flow nasal cannula.

MV, Mechanical ventilation.

P-SILI, self-inflicted lung injury by the patient.

RT-PCR, reverse transcriptase polymerase chain reaction.

Crs, Respiratory system compliance.

PEEP, Positive end-expiratory pressure

ECMO, extracorporeal membrane oxygenation.

APACHE, Acute Physiology and Chronic Health Evaluation.

SOFA, Sequential Organ Failure Assessment.

ACE inhibitors, angiotensin converting enzyme inhibitors.

Declarations

Ethics approval and consent to participate

The Institutional Ethics Committee approved this project (Research Ethics Committee Nº 200504004, Faculty of Medicine, Pontificia Universidad Católica de Chile), and waived the need for informed consent.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

MV and RC are guarantors of the entire manuscript; MV, RC, EK, GH and GB

designed the study; MV, EK, BL, PB, ER, AN, IR, MA, EE, LR, GH and RC collected and analyzed all the data. All the authors helped in the data interpretation and the manuscript draft. All authors read and approved the final manuscript.

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