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CLINICAL CHARACTERISTICS OF CRITICALLY ILL PATIENTS WITH COVID-19

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Abstract Coronavirus disease 2019 (COVID-19) pandemic poses a major challenge for healthcare systems. In South America, local information about the incidence and clinical characteristics of critically ill patients diagnosed with COVID-19 is still limited. In this observational and retrospective study, we aimed to describe critically ill patients' clinical and respiratory characteristics with COVID-19. The study was performed over 6 months in an intensive care unit (ICU) of a high complexity hospital in Buenos Aires, Argentina. Patients older than 18 years with laboratory-confirmed COVID-19 by reverse transcriptase-polymerase chain reaction (RT-PCR) for SARS-CoV-2 were included in the study. Demographic characteristics such as sex and age, comorbidities, laboratory results, imaging results, ventilatory mechanics data, complications, and mortality were recorded. A total of 168 critically ill patients with COVID-19 were included. Sixty-six percent were men with a median age of 65 years (58-75); 79.7% had at least one comorbidity. The most frequent comorbidity was arterial hypertension, affecting 52.4%. A 67.9% required invasive mechanical ventilation (MV), and no one was treated with non-invasive ventilation. Most of the patients in MV (73.7%) required neuromuscular blockade due to severe hypoxemia. A 36% was ventilated in the prone position. The length of stay in the ICU was 13 days (6-24) and ICU's mortality was 25%.

Key words: COVID-19, SARS-CoV-2, intensive care, pandemic, Argentina, South America

Resumen ***Características clínicas de los pacientes críticos con COVID-19.*** La pandemia de la enfermedad por coronavirus 2019 (COVID-19) plantea un gran desafío para los sistemas de salud. En América del Sur, la información local sobre la incidencia y las características clínicas de los pacientes críticamente enfermos diagnosticados con COVID-19 aún es limitada. En este estudio observacional y retrospectivo, nuestro objetivo fue describir las características clínicas y respiratorias de los pacientes críticamente enfermos con COVID-19. El estudio se realizó durante 6 meses en una unidad de cuidados intensivos (UCI) de un hospital de alta complejidad en Buenos Aires, Argentina. Se incluyeron en el estudio pacientes mayores de 18 años con COVID-19 confirmado por laboratorio mediante la reacción en cadena de la polimerasa con transcriptasa inversa (RT-PCR) para SARS-CoV-2. Se registraron características demográficas como sexo y edad, comorbilidades, resultados de laboratorio, resultados de imagen, datos de mecánica ventilatoria, complicaciones y mortalidad. Se incluyeron un total de 168 pacientes críticamente enfermos con COVID-19. El 66% eran hombres con una mediana de edad de 65 años (58-75). El 79.7% presentaba al menos una comorbilidad. La comorbilidad más frecuente fue la hipertensión arterial, afectando al 52.4%. El 67.9% requirió ventilación mecánica invasiva (VM) y ninguno fue tratado con ventilación no invasiva. La mayoría de los pacientes en VM (73.7%) requirieron bloqueo neuromuscular por hipoxemia grave. Un 36% de ellos fueron ventilados en decúbito prono. La estancia en UCI fue de 13 días (6-24) y la mortalidad en UCI fue del 25%.

Palabras clave: COVID-19, SARS-CoV-2, cuidados intensivos, pandemia, Argentina, América del Sur

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KEY POINTS
Current knowledge

- Coronavirus disease 2019 (COVID-19) pandemic poses a major challenge for healthcare systems. In South America, local information about the incidence and clinical characteristics of critically ill patients diagnosed with COVID-19 is still limited.

Article´s contribution to knowledge

- The most frequent comorbidity was arterial hypertension, affecting 52.4% of 168 patients, followed by obesity in 41.6% (70).
- A 67.9% required invasive mechanical ventilation.
- The length of stay in the ICU was 13 days (6-24) and the mortality in the ICU was 25%.

In December 2019, a new coronavirus was identified by the Chinese Center for Disease Control and Prevention. On March 11th of 2020, the World Health Organization (WHO) declared the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak as a pandemic due to the constantly increasing number of cases outside China[1]. Up to date, SARS-CoV-2 affected more than 32 million people over the world and caused 1 million deaths.

On March 3rd, 2020, 64 days after the first case was reported in China, a case in Argentina was confirmed. Since then, the number of cases gently ascended[2]; up to September 30th, 2020, a total of 736 609 had tested positive for the new SARS-CoV-2, with 139 419 active cases, and 3792 (2.7%) admitted to intensive care unit (ICU)[3].

Nevertheless, local information about the incidence and clinical characteristics of critically ill patients diagnosed with COVID-19 is still limited[4]. In this context, knowledge of critically ill patients' baseline characteristics and outcomes is crucial for health and government officials engaged in planning efforts to address local outbreaks. This case series describes clinical characteristics, image findings and respiratory mechanics of COVID-19 patients admitted to ICU in a high complexity hospital in Buenos Aires.

Materials and methods

For this retrospective single-center study, ICU patients were recruited between March 15th, 2020 and September 15th, 2020. Data were obtained from medical records of adult patients (18 years of age or older) with laboratory-confirmed COVID-19 hospitalized in the ICU in a high complexity hospital in Buenos Aires. Those with adequacy of the therapeutic effort at ICU admission were excluded.

According to WHO guidance[5], laboratory confirmation for SARS-CoV-2 was obtained as a positive result of real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay of nasopharyngeal swabs. Only laboratory-confirmed cases were included in the analysis, and the Hospital Ethics Committee approved the study in March 2019. Epidemiological, demographic, clinical, laboratory, respiratory support, and outcome data were obtained. Radiologic assessment of chest x-rays and all laboratory testing was performed according to the treating physician criteria. The presence of a radiologic abnormality was determined and the Radiographic Assessment of Lung Edema (RALE) score[6] was calculated and reviewed by medical imaging specialists. Laboratory assessment consisted of a complete blood count, a blood chemical analysis, coagulation testing, assessment of liver and renal function, and measure of electrolytes, C-reactive protein (CRP), procalcitonin, pro b-type natriuretic peptide (pro-BNP), lactate dehydrogenase, high-sensitivity cardiac troponin (hs-cTnT), d-dimer, ferritin and interleukin-6 (IL-6).

The number of patients who died or been discharged, and those that stayed in ICU until September 30th of 2020 was recorded. Additionally, ICU length of stay was determined.

No statistical sample size calculation was performed in advance and the sample size was equal to the number of patients treated during the study period. Continuous variables were expressed as medians and interquartile ranges or simple ranges, as appropriate. Categorical variables were summarized as counts and percentages.

No imputation was made for missing data. Mann-Whitney rank-sum test was used to compare nonparametric continuous variables. χ^2 or Fisher exact test was used for categorical variables as appropriate. All statistical tests were 2-tailed, and statistical significance was defined as $p < .05$. The analysis has not been adjusted for multiple comparisons, and given the possibility of a type I error, the findings should be interpreted as exploratory and descriptive. All the analyses were performed using R Software, version 3.6.2 (R Foundation for Statistical Computing).

Results

Between March 15th and September 15th of 2020, a total of 259 patients with suspected COVID-19 were referred to the ICU. A total of 87 with negative test results for SARS-CoV-2 were not included in the study. Additionally, four with laboratory-confirmed COVID-19 but without the adequacy of therapeutic effort at ICU admission were excluded. Thus, data from 168 critically ill patients with laboratory-confirmed COVID-19 was analyzed.

Overall, 66% (111) patients were male, with a median age of 67 (58-75). Eighty percent (134) presented at least one comorbidity. Hypertension was the most common comorbidity, affecting 52.4% (88), followed by obesity in 41.6% (70). The 6.5% (11) admitted were health-care workers. Table 1 shows the demographic and clinical characteristics of the patients.

The median (IQR) time between symptoms onset and hospital admission was 4 days (2-7). Fever was referred by 91.1% (153) followed by shortness of breath (52.4% [88]). The main ICU admission criteria were clinical monitoring (59.5% [100]), and 40.5% (68) needed MV at ICU arrival. The median time up to ICU admission was seven days (4-9) since symptoms onset.

All patients had chest x-rays at ICU admission, 98.2% (165) revealed abnormal results. The most common pattern on chest x-rays was patchy bilateral shadowing in

TABLE 1.– *Patients characteristics*

	All patients (n = 168)	Non-MV Survivors (n = 54)	MV Survivors (n = 68)	MV Non-survivors (n = 46)
Demographic data				
Male, n (%)	111 (66)	36 (66.6)	45 (66.2)	30 (65.2)
Age, median (IQR), y	67 (58-75)	61 (54 -73)	65 (59-73)	71 (65-78)
Distribution, n (%)				
≤ 39 yearse	8 (4.7)	5 (9.2)	2 (2.9)	1 (2.1)
40-59 years	44 (26.1)	19 (35.1)	17 (25)	8 (17.3)
60-79 years	96 (57.1)	27 (50)	43 (63.2)	26 (56.5)
≥ 80 years	20 (11.9)	3 (5.5)	6 (8.8)	11 (23.9)
Scores, median (IQR)				
APACHE II score	10 (6-14)	5 (3-10)	11 (9-15)	13 (10-17)
SOFA score day 1	2 (2-5)	1 (1-2)	3 (2-5)	4 (2-5)
SOFA score day 3	2 (1-5)	1 (1-2)	3 (2-6)	3 (2-6)
SOFA score day 5	3 (1-4)	0 (0-1)	3 (2-4)	3 (2-4)
Charlson score	4 (2-5)	3 (1-5)	4 (2-5)	5 (4-7)
Comorbidities, n (%)				
Hypertension	88 (52.4)	26 (48.1)	34 (50)	28 (60)
Angiotensin-converting-enzyme inhibitors use	31 (18.4)	11 (20.4)	14 (20.6)	6 (13)
Angiotensin II receptor blocker use	24 (14.3)	6 (11.1)	7 (10.3)	11 (23.9)
Obesity	70 (41.6)	25 (46.2)	29 (42.6)	16 (34.8)
Diabetes	31 (18.5)	12 (22.2)	10 (14.7)	9 (19.6)
Immunosuppression	26 (15.5)	7 (13)	6 (8.8)	13 (28.3)
Active oncological disease without chemotherapy	14 (8.3)	6 (11.3)	3 (4.5)	5 (10.9)
Chronic use of corticosteroids	11 (6.5)	2 (3.7)	4 (5.9)	5 (10.9)
Active oncological disease with chemotherapy)	9 (5.4)	2 (3.7)	1 (1.5)	6 (13)
Solid organ transplant	9 (5.4)	2 (3.7)	2 (2.9)	5 (10.9)
Coronary heart disease	24 (14.3)	7 (13)	10 (14.7)	7 (15.2)
Chronic kidney disease	20 (11.9)	4 (7.4)	8 (11.8)	8 (17.4)
Active smoking	18 (10.7)	5 (9.3)	8 (11.8)	5 (10.9)
COPD	10 (6)	3 (5.6)	2 (2.9)	5 (10.9)
Asthma	9 (5.4)	3 (5.6)	5 (7.4)	1 (2.2)
Congestive heart failure	5 (3)	2 (3.8)	2 (2.9)	1 (2.2)
Epidemiological link, n (%)				
Community transmission	140 (83.3)	44 (81.4)	58 (85.2)	38 (82.6)
In-hospital transmission	24 (14.3)	8 (14.8)	8 (11.7)	8 (17.4)
Imported cases	4 (2.4)	2 (3.7)	2 (3.7)	0
ICU admission criteria, n (%)				
Clinical monitoring	100 (59.5)	54 (100)	31 (46.3)	15 (32.6)
Respiratory support	68 (40.5)	0	37 (45.6)	31 (67.4)

MV: mechanical ventilation; APACHE II: Acute Physiology and Chronic Health Disease Classification System II; SOFA: Sequential Organ Failure Assessment; COPD: chronic obstructive pulmonary disease

72% (121) with a median (IQR) RALE score of 7 (4-7). The presence of pleural effusion was infrequent (9.5% [16] of chest x-rays).

On ICU admission, lymphocytopenia was present in 73.2% (123), thrombocytopenia in 19.6% (33), and leukopenia in 6.5% (11).

Among mechanical ventilation (MV) survivors and MV non-survivors, no difference was found in total leukocyte count (median [IQR], 7292 mm^3 [5867-9847] in MV survivors vs. 9004 mm^3 [6455-12 819] in MV non-survivors; p = 0.1313) nor absolute neutrophil count (median [IQR], 6034 mm^3 [4319-7827] in MV survivors vs. 7609 mm^3 [5238-10 980] in MV non-survivors; p = 0.3366).

Regarding lymphocytes, absolute cell count was significantly higher among non-MV patients than MV patients (median [IQR], 867 mm^3 [571-1148] vs. 668 mm^3 [461-1005]; p = 0.0042), and also, a significantly higher count was registered in MV survivors than MV non-survivors (499 mm^3 in non-MV [352-862]; p = 0.0294).

Neutrophil to lymphocyte ratio (NLR) was higher among non-MV patients than MV survivors in ventilated vs. non-ventilated (median [IQR], 6.9 [4.5-11.8] vs. 11.3 [5.5-24.2]; p = 0.0059) but non difference was found between MV survivors vs. MV non-survivors (median [IQR], 11,2 [6,3-22,4] vs. 12,9 [4,9-25,3]; p = 0.9913).

The majority of patients had elevated levels of inflammatory biomarkers like CRP, ferritin and IL-6. ProBNP was higher among ventilated vs. non-ventilated (median [IQR], 520 pg/ml [199-1189] vs. 172 [49-526]; p = 0.0004). Also, among overall, non-surviving patients had more prominent laboratory abnormalities including proBNP and d-dimer than survivors (median [IQR], 690 pg/ml [362-2062] vs. 435 pg/ml [128-939]; p = 0.0106 and 1158 ng/ml [826-1817] vs. ng/ml 818 [618-1305]; p = 0.0097). Table 2 shows the radiologic and laboratory findings at ICU admission. Figure 1 shows laboratory results among non-MV, patients, MV survivors and MV non-survivors.

A total of 114 patients (67.9%) required endotracheal intubation and invasive MV. No one was treated with noninvasive ventilation. On the first day of MV, the median positive end-expiratory pressure (PEEP) was 10 (8-11) cm H_2O. PEEP levels as high as 16 cm H_2O were applied. Among a total of 114 patients, 75 (65.7%) required a fraction of inspired oxygen (FIO2) of at least 50%, and 11 (9.4%) required 100% FIO2. The median PaO2/FIO2 ratio was 200 (IQR, 147-268). Also, lower PaO2/FIO2 ratios on the first day of MV were registered among non-survivors vs. survivors (median [IQR], 180 [120-214] vs. 216 [167-290]; p = 0.0309). All MV patients fulfilled Berlin criteria for Acute respiratory distress syndrome (ARDS)[7].

Regarding respiratory mechanics, the median plateau pressure (P_{plat}) on the first day of MV was 22 (19-24) cm H_2O, the median driving pressure (ΔP) was 11 (10-14) cm H_2O and the median respiratory system compliance (Crs) was 36 (30-47) ml/cm H_2O.

A majority of the mechanically ventilated patients (84 [73.7%]) required neuromuscular blockade due to severe hypoxemia to avoid patient-ventilator asynchronies. Also, prone position ventilation was applied to 41 (36%), and 36.1% of them (15) required more than one prone positioning session. Twelve patients (10.5%) received inhaled nitric oxide (iNO) and 6 (5.7%) were connected to veno-venous extracorporeal membrane oxygenation (V-V ECMO) because of refractory hypoxemia.

The time elapsed of MV was 16 days (19-30) among overall ventilated patients and 8 days (6-14) among those who were successfully extubated (26 [22.8%]). Thirty-two patients (28.1%) underwent percutaneous tracheostomy due to prolonged weaning. The median time of MV until tracheostomy was 20 days (15-27); 10 patients (8.7%) remained under MV at data cut off. Table 3 shows respiratory mechanics, oxygenation parameters and adjunctive therapies applied.

Most of the patients received dexamethasone (on RECOVERY-trial dose[8]) and empirical intravenous antibiotic therapy (143 [85.1%] and 133 [79.2%], respectively). Ninety patients (53.6%) were included in a 2:1 blinded-protocol of convalescent plasma against placebo. Other treatments like ritonavir/lopinavir (23 [13.7%]) and tocilizumab (3 [1.8%]) were less frequently applied.

A common ICU related complication was delirium that was identified in 121 patients (72%) overall. Delirium was less present among non-ventilated (23 [42.5%]) in comparison with ventilated that survived (61 [89.7%]) and those who died (37 [80.4%]). Other complications registered were catheter-related sepsis (23 [13.7%]), pressure ulcers (17 [20.1%]), urosepsis (10 [6%]) and ventilator-associated pneumonia (11 [6.5%])

Among overall patients, the median duration of hospitalization was 21 days (14-32) and the median length of stay in ICU was 13 days (6-24). ICU length of stay among survivors was 5 days (3-8) for non-ventilated patients and 23 days (16-31) for those who required invasive MV. Overall ICU mortality of this series was 25% (42). Table 4 shows treatments, ICU related complications, and clinical outcomes at data cutoff.

Discussion

The population in this study mainly consisted of men (66%) with a median age of 67 (58-75) years, which is substantially high compared to the median age of all the positive Argentinian cases of COVID-19 (38 years old)[9]. The previous suggests that gender and age are risk factors for admission to the ICU, as previously reported[10]. Moreover, in this cohort, most of the patients (79.7%) had at least one comorbidity, with a large proportion with hypertension (52.4%) and obesity (41,6%).

TABLE 2.– *Radiologic and laboratory findings at intensive care unit admission*

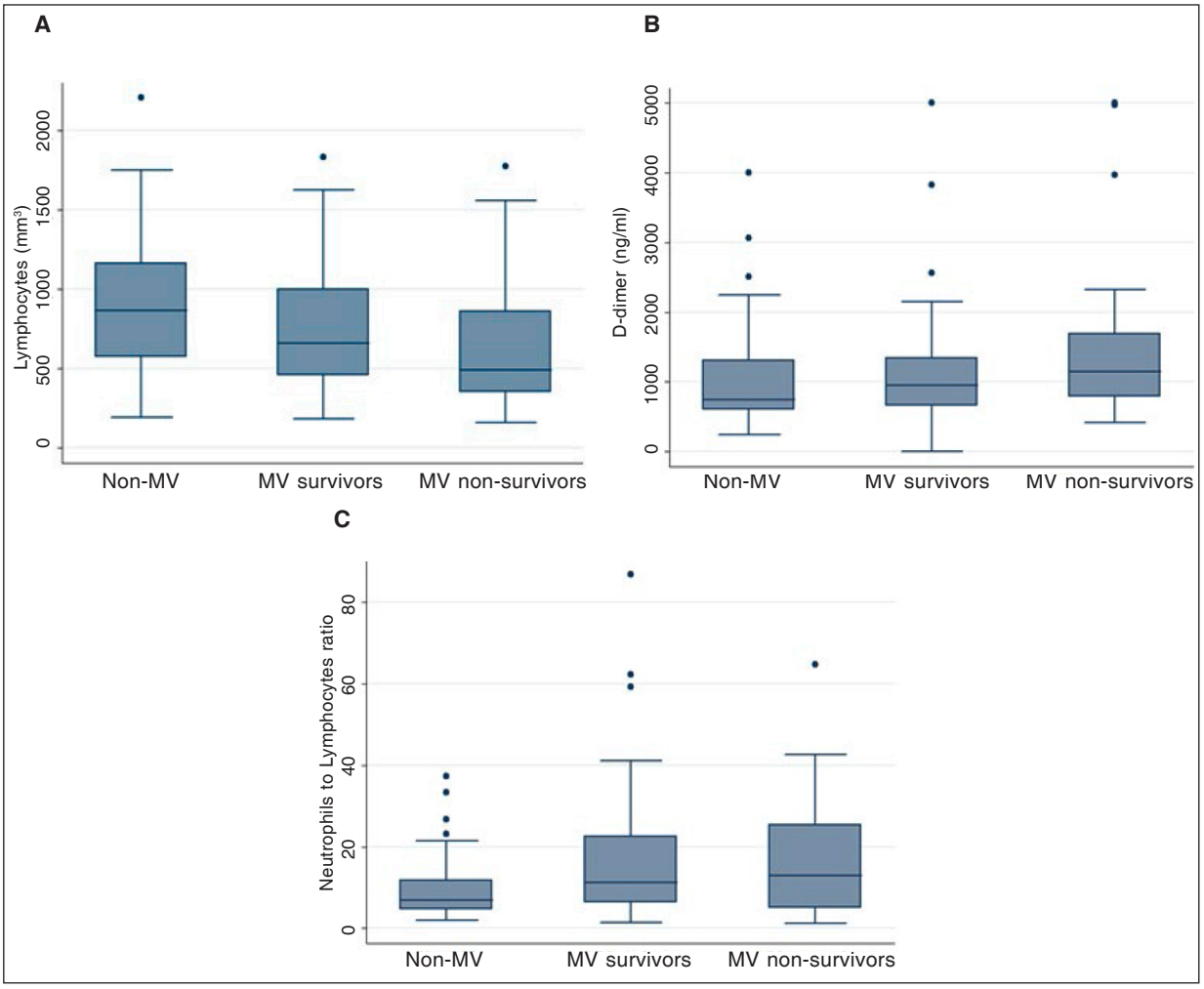
	All patients (n = 168)	Non-MV Survivors (n = 54)	MV Survivors (n = 68)	MV Non-survivors (n = 46)
Radiologic findings				
RALE score	7 (4-7)	6 (3-7)	7 (4-7)	7 (5-7)
Bilateral compromise, n (%)	121 (78)	35 (64.8)	49 (72.1)	37 (80.4)
Pleural effusion, n (%)	16 (9.5)	0	9 (13.2)	7 (15.2)
Laboratory findings, median (IQR)				
Hematocrit, %	38 (34-42)	40 (36-42)	37 (34-41)	38 (34-41)
Leukocytes, per mm^3	8001 (5844-11713)	7292 (5867-9847)	9004 (6455-12819)	7733 (5095-12 688)
Neutrophils, per mm^3	6560 (4464-10386)	6034 (4319-7827)	7609 (5238-10980)	6302 (3901-11477)
Lymphocytes, per mm^3	695 (456-1010)	867 (571-1148)	668 (461-1005)	499 (352-862)
Neutrophils to lymphocytes ratio	9.5 (5.1-19.6)	6.9 (4.5-11.8)	11.2 (6.3-22.4)	12.9 (4.9-25.3)
Platelets, per mm^3	205 000 (154 000-267 900)	209 200 (169 625-266 225)	221 100 (169 750-280 400)	193 200 (142 800-231 525)
Serum creatinine, mg/dl	0.90 (0.71-1.18)	0.83 (0.65-1.15)	0.94 (0.71-1.12)	1.05 (0.78-1.39)
Serum urea, mg/dl	42 (31-57)	37 (27-49)	43 (32-58)	47 (37-64)
Sodium, mmol/l	135 (133-138)	135 (132-137)	136 (134-138)	135 (133-139)
Potassium, mmol/l	3.9 (3.7-4.4)	3.8 (3.6-4.3)	3.9 (3.6-4.4)	4.0 (3.7-4.5)
Chloride, mmol/l	102 (98-105)	101 (98-103)	103 (100-106)	102 (98-106)
Total bilirubin, mg/dl	0.58 (0.42-0.72)	0.60 (0.47-0.74)	0.58 (0.39-0.66)	0.58 (0.42-0.88)
ALP, UI/l	65 (52-89)	61 (48-87)	65 (52-80)	75 (52-128)
AST, UI/l	35 (27-48)	33 (23-47)	33 (25-48)	38 (26-56)
ALT, UI/l	29 (17-52)	33 (18-58)	26 (17-49)	29 (17-45)
Albumin, g/dl	3.37 (3.06-3.6)	3.46 (3.26-3.80)	3.23 (3.00-3.48)	3.30 (2.94-3.58)
Prothrombin time, s	85 (74-94)	86 (78-93)	85 (76-95)	79 (64-94)
Procalcitonin, ng/ml[a]	0.24 (0.09-0.66)	0.17 (0.07-0.33)	0.31 (0.09-0.61)	0.36 (0.14-1.87)
pro-BNP, pg/m[b]	435 (118-1045)	172 (49-526)	435 (128-939)	690 (362-2062)
hs-cTnT, pg/mL[c]	14 (8-32)	10 (7-16)	13 (8-25)	31 (14-92)
D-Dimer, ng/ml[d]	945 (669-1529)	740 (608-1300)	947 (658-1344)	1158 (826-1817)
C-reactive protein, mg/l[e]	93 (51-151)	82 (51-105)	109 (59-140)	99 (49-177)
Ferritin, g/ml[f]	723 (384-1249)	632 (267-1356)	741 (409-1244)	668 (422-1024)
Lactate dehydrogenase, UI/l[g]	300 (256-355)	264 (209-320)	321 (272-379)	313 (263-418)
Interleukin 6, pg/ml[h]	55 (13-114)	55 (11-104)	48 (18-137)	110 (14-271)

MV: mechanical ventilation; RALE: radiographic assessment of lung edema; ALP: alkaline phosphatase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; pro-BNP: pro b-type natriuretic peptide; hs-cTnT: high-sensitivity cardiac troponin

[a]Data regarding procalcitonin were missing for 40 patients (24%). [b]Data regarding pro-BNP were missing for 26 patients (15%). [c]Data regarding hs-cTnT were missing for 74 patients (44%). [d]Data regarding D-dimer were missing for 41 patients (24%). [e]Data regarding C-reactive protein were missing for 80 patients (48%). [f]Data regarding ferritin were missing for 77 patients (46%). [g]Data regarding lactate dehydrogenase were missing for 96 patients (57%). [h]Data regarding interleukin 6 were missing for 128 patients (76%)

In this case series, most patients were admitted to the ICU because of acute hypoxemic respiratory failure that required clinical monitoring. A substantial proportion of patients needed respiratory support and endotracheal intubation at ICU arrival. Endotracheal intubation and invasive MV were needed in 67.9%, whereas only 32.1% could be managed with oxygen delivery by a non-rebreather mask. Setting primary focus on health-care personnel security, no patient received non-invasive MV (eg. continuous positive airway pressure, non-invasive positive pressure ventilation, or high flow nasal cannula) due to the risk of aerosol dispersion[11]. There is still controversy regarding the efficacy of non-invasive MV devices to avoid endotracheal intubation[12] but the need for invasive MV in this patient population under study was similar to other ICUs where non-invasive MV was applied: 65% (São Paulo, Brazil)[13], 71% (Washington State, USA)[14], 71% (Wuhan, China)[15], 80.8% (Detroit,

Fig. 1.– Laboratory results among non-mechanically ventilated (non-MV) patients, MV survivors and MV non-survivors of. A: lymphocytes (per mm3). B: D-dimer (ng/ml). C: neutrophils to lymphocytes ratio



USA)[16], 88% (Lombardy region, Italy)[17], 96.7% (Mexico City, Mexico)[18].

Among ventilated patients, 44.7% (51) presented paO2/FiO2 lower than 200 on the first day of MV, although pulmonary mechanics were almost normal (median P_{plat} 22 cm H_2O [19-24] and median ΔP 11 cm H_2O [10-14]). Nevertheless, 79.8% (91) had low Crs(<50 ml/cm H_2O) with a median Crs of 36 ml/cm H_2O (30-47) despite of lung-protective ventilation (tidal volume ≤ 8 ml/kg predicted body-weight). These findings are in accordance with information that reported that COVID-19 ARDS respiratory features are similar to non-COVID-19 ARDS[19]. Additionally, the values of Crs, Pplat, and ΔP were very similar to previously published cohorts of non-COVID-19 ARDS patients[20].

Due to refractory hypoxemia, six patients (5.7%) were connected to V-V ECMO. Despite the middle-income country circumstances and the low volume of the ECMO program patients, outcomes are comparable to international series. ECMO survival and survival to discharge was 66% and 50%, respectively[21-23].

Since patients required MV for an extended period time due to prolonged weaning, there were more than underwent percutaneous tracheostomy compared to those who were successfully extubated (32 [28.1%] and 26 [22.8%], respectively). At the beginning of the pandemic, several scientific societies warned about a possible increase in the request for tracheostomies related to SARS-CoV-2 infection[24-26, 29]. The need for tracheostomies in critically ill COVID-19 patients ranges from 36% to 53%, according to the data found in the literature[27–29].

Prioritizing the protection of health personnel, tracheostomy was considered possible only in those who were expected to obtain a substantial benefit. Ideally, it was performed 21 days after intubation with a negative RT-PCR test[30]. Following that criteria and up to data cut-

TABLE 3.– *Respiratory mechanics, oxygenation parameters and adjunctive therapies applied*

	All patients (n = 114)	MV Survivors (n = 68)	Non-survivors (n = 46)
Respiratory mechanics, median (IQR)			
Day 1			
FiO_2, %	50 (40-60)	50 (40-60)	60 (50-70)
PaO_2/FiO_2	201 (147-268)	217 (167-290)	180 (120-214)
Tidal volume, ml/kg of predicted body weight	7.3 (6.9-7.4)	7.3 (7.0-7-5)	7.2 (6.6-7.4)
PEEP, cm H_2O	10 (8-12)	10 (8-12)	9 (8-10)
Pplat, cm H_2O	22 (19-24)	21 (18-23)	22 (20-24)
ΔP, cm H_2O	11 (10-14)	11 (10-13)	12 (10-14)
Cstat, ml/cm H_2O	36.2 (29.4-47.2)	37.8 (30.0-47.8)	35.0 (28.5-40.0)
Day 3			
FiO_2, %	40 (35-50)	40 (35-45)	40 (40-50)
PaO_2/FiO_2	233 (192-285)	252 (196-300)	216 (174-259)
Tidal volume, ml/kg of predicted body weight	7.4 (7.1-8.0)	7.5 (7.0-8.0)	7.4 (6.9-7.7)
PEEP, cm H_2O	10 (8-12)	10 (8-12)	8 (8-12)
Pplat, cm H_2O	22 (20-24)	22 (20-23)	22 (20-25)
ΔP, cm H_2O	11 (10-13)	10 (10-12)	11 (10-13)
Cstat, ml/cm H_2O	40.0 (30.9-47.4)	41.8 (32.4-47.9)	37.4 (30.2-43.3)
Day 5			
FiO_2, %	40 (35-50)	40 (35-45)	45 (40-50)
PaO_2/FiO_2	225 (180-271)	229 (206-287)	205 (160-233)
Tidal volume, mL/kg of predicted body weight	7.6 (7.3-8.0)	7.8 (7.3-8.0)	7.4 (7.2-7.9)
PEEP, cm H_2O	8 (8-12)	8 (8-12)	8 (8-10)
Pplat, cm H_2O	21 (19-23)	22 (19-23)	21 (19-22)
ΔP, cm H_2O	10 (10-12)	11 (10-12)	10 (10-12)
Cstat, ml/cm H_2O	42.7 (34.1-49.4)	42.7 (35.8-50.5)	42.7 (34.0-48.0)
Adjunctive therapies, no. (%)			
Neuromuscular blockade	84 (73,7%)	50 (73,5%)	34 (73,9%)
Prone positioning	41 (36%)	25 (36,8%)	16 (34,8%)
iNO	12 (10,5%)	8 (11,8%)	4 (8,7%)
V-V ECMO	6 (5,7%)	3 (4,4%)	3 (6,5%)
Weaning			
Extubated, n (%)	26 (22.8)	26 (38.2)	0
Tracheostomy, n (%)	32 (28.1)	27 (39.7)	5 (10.9)
Days until tracheostomy, median (IQR)	20 (15-27)	19 (15-25)	27 (10-32)
Days of MV, median (IQR)	16 (19-30)	20 (11-33)	13 (7-26)

MV: mechanical ventilation; FiO_2: fraction of inspired oxygen; PaO_2: partial pressure of oxygen; PEEP: positive end-expiratory pressure; Pplat: plateau pressure; ΔP: driving pressure; Crs: respiratory system compliance; iNO: inhaled nitric oxide; V-V ECMO: veno-venous extracorporeal membrane oxygenation

off, none of the surgeons or intensivists who performed tracheostomies developed symptoms or tested positive for COVID-19. Nevertheless, a longer time of MV prior to tracheostomy was observed in relation to a previous series from the same center in a non-pandemic scenario (median 20 days [15-27] and 9 days [6-12], respectively)[31].

ICU mortality rate was slightly lower than a recent systematic review and meta□analysis of observational studies that informed a 41.6% (34.0-49.7) ICU mortality rate across international studies. This could be explained because, optimistically, countries in the later phase of the pandemic may be coping better with COVID-19[32].

TABLE 4.– *Treatment, intensive care unit related complications and clinical outcomes*

	All patients (n = 168)	Non-MV Survivors (n = 54)	MV Survivors (n = 68)	MV Non-survivors (n = 46)
Treatment				
Dexamethasone, n (%)	143 (85.1)	44 (81.4)	59 (86.8)	40 (87)
Empirical antibiotic, n (%)	133 (79.2)	35 (64.8)	56 (82.4)	42 (91.3)
Convalescent plasma protocol, n (%)	90 (53.6)	40 (74)	32 (47.1)	18 (39.1)
Ritonavir / lopinavir, n (%)	23 (13.7)	5 (9.2)	12 (17.6)	6 (13)
Tocilizumab, n (%)	3 (1.8)	1 (1.8)	1 (1.5)	1 (2.2)
ICU related complications				
Delirium, n (%)	121 (72)	23 (42.5)	61 (89.7)	37 (80.4)
Catheter-related sepsis, n (%)	23 (13.7)	0	14 (20.6)	9 (19.6)
Pressure ulcers, no. (%)	17 (20.1)	0	8 (11.8)	9 (19.6)
Ventilator-associated pneumonia, n (%)	11 (6.5)	0	3 (4.4)	8 (17.3)
Urosepsis, n (%)	10 (6)	0	4 (5.9)	6 (13.3)
Pneumothorax, n (%)	5 (2.9)	1 (1.8)	1 (1.4)	3 (6.5)
Pulmonary embolism, n (%)	5 (2.9)	1 (1.8)	1 (1.4)	3 (6.5)
Clinical outcomes at data cutoff				
ICU length of stay	13 (6-24)	5 (3-8)	23 (16-31)	13 (8-21)
Hospital length of stay	21 (14-32)	15 (11-23)	31 (23-42)	17 (13-27)
Remained in hospital, n (%)	28 (16.7)	0	28 (41.2)	0
Remained in ICU, n (%)	18 (10.7)	0	18 (26.5)	0
ICU mortality, n (%)	42 (25)	0	0	43 (91.3)
Hospital mortality, n (%)	46 (27.4)	0	0	100% (46)

MV: mechanical ventilation; ICU: intensive care unit

Although this study is considered limited due to the relatively small number of patients from a single center and could not be broadly applicable to other patients with a critical illness, it provides initial experience regarding characteristics of COVID-19 in those with critical illness in Argentina.

Final disclosure: Our study was initially released in medRxiv as a preprint[33].

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References

1. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. In:*https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020*; accessed September 2020.
2. Gemelli NA. Management of COVID-19 outbreak in Argentina: the beginning. *Disaster Med Public Health Prep* 2020; 14:815-7.
3. Ministerio de Salud de la Nación. In: *https://www.argentina.gob.ar/coronavirus/informes-diarios/reportes/septiembre2020*; accessed September 2020.
4. Carboni Bisso I, Huespe I, Lockhart C, et al. [COVID-19 en la terapia intensiva. Análisis de la experiencia durante el primer mes de la pandemia]. *Medicina (B Aires)* 2020; 80 Suppl 3: 25–30.
5. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected. In: *https://apps.who.int/iris/handle/10665/330854*; accessed September 2020.
6. Jabaudon M, Audard J, Jaber S, et al. The radiographic assessment of lung edema (RALE) score is associated with survival and may be useful to identify focal and non-focal lung imaging phenotypes in patients with ARDS. *Am J Resp Crit Care* 2020; 201: A1133. doi.org/ 10.1164/ajrccm-conference.2020.201.1_MeetingAbstracts.a1133.
7. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012; 307: 2526–33.
8. The RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with Covid-19.*N Engl J Med*2021; 384:693-704.
9. Ministerio de Salud de la Nación. In: *https://www.argentina.gob.ar/sites/default/files/sala_29_09_.pdf* ; accessed September 2020.
10. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020; 584: 430–6.

11. Ferioli M, Cisternino C, Leo V, Pisani L, Palange P, Nava S. Protecting healthcare workers from SARS-CoV-2 infection: practical indications. *Eur Respir Rev* 2020; 29: 200068.
12. Agarwal A, Basmaji J, Muttalib F, et al. High-flow nasal cannula for acute hypoxemic respiratory failure in patients with COVID-19: systematic reviews of effectiveness and its risks of aerosolization, dispersion, and infection transmission. *Can J Anaesth* 2020; 67: 1217-48.
13. Teich VD, Klajner S, Almeida FAS de, et al. Epidemiologic and clinical features of patients with COVID-19 in Brazil. *Einstein* 2020; 18: eAO6022.
14. Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. *JAMA* 2020; 323: 1612–4.
15. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020; 8: 475-81.
16. Suleyman G, Fadel RA, Malette KM, et al. Clinical characteristics and morbidity associated with coronavirus disease 2019 in a series of patients in Metropolitan Detroit. *JAMA Network Open* 2020; 3: e2012270.
17. Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. *JAMA* 2020; 323: 1574-81.
18. Mendez-Probst CE, Velázquez-Fernández D, Castillejos-Molina R. Clinical and epidemiological characteristics of patients diagnosed with COVID-19 in a tertiary care center in Mexico City: A prospective cohort study. *Rev Invest Clin* 2020; 72: 250.
19. Ferrando C, Suarez-Sipmann F, Mellado-Artigas R, et al. Clinical features, ventilatory management, and outcome of ARDS caused by COVID-19 are similar to other causes of ARDS. *Intensive Care Med* 2020; 46: 2200-11.
20. Bellani G, Laffey JG, Pham T, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA* 2016; 315: 788-800.
21. Laffey JG, Madotto F, Bellani G, et al. Geo-economic variations in epidemiology, patterns of care, and outcomes in patients with acute respiratory distress syndrome: insights from the LUNG SAFE prospective cohort study. *Lancet Respir Med* 2017; 5: 627-38.
22. Riera J, Argudo E, Martínez-Martínez M, et al. Extracorporeal membrane oxygenation retrieval in coronavirus disease 2019: a case-series of 19 patients supported at a high-volume extracorporeal membrane oxygenation center. *Crit Care Explor* 2020; 2: e0228.
23. Schmidt M, Hajage D, Lebreton G, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome associated with COVID-19: a retrospective cohort study. *Lancet Respir Med* 2020 8: 1121-31.
24. Tracheostomy guidance during the COVID-19 Pandemic. In: *https://www.entuk.org/tracheostomy-guidance-during-covid-19-pandemic*; accessed October 2020.
25. Ralli M, Greco A, de Vincentiis M. The Effects of the COVID-19/SARS-CoV-2 pandemic outbreak on otolaryngology activity in Italy. *Ear Nose Throat J* 2020; 145561320923893.
26. Piazza C, Filauro M, Dikkers FG, et al. Long-term intubation and high rate of tracheostomy in COVID-19 patients might determine an unprecedented increase of airway stenoses: a call to action from the European Laryngological Society. *Eur Arch Otorhinolaryngol* 2021; 278: 1-7.
27. Angel L, Kon ZN, Chang SH, et al. Novel percutaneous tracheostomy for critically ill patients with covid-19. *Ann ThoracSurg* 2020; 110: 1006-11.
28. Picetti E, Fornaciari A, Taccone FS, et al. Safety of bedside surgical tracheostomy during COVID-19 pandemic: A retrospective observational study. *PLoS One* 2020; 15: e0240014.
29. Volo T, Stritoni P, Battel I, et al. Elective tracheostomy during COVID-19 outbreak: to whom, when, how? Early experience from Venice, Italy. *Eur Arch Otorhinolaryngol* 2021; 278: 781-9.
30. Smith D, Montagne J, Raices M, et al. Tracheostomy in the intensive care unit: Guidelines during COVID-19 worldwide pandemic. *Am J Otolaryngol* 2020; 41: 102578.
31. Carboni Bisso I, Huespe I, Schverdfinger S, et al. Traqueostomía percutánea guiada por broncoscopía: experiencia en 235 procedimientos. *Revista de la Facultad de Ciencias Médicas de Córdoba* 2020; 77: 187-90.
32. Armstrong RA, Kane AD, Cook TM. Outcomes from intensive care in patients with COVID-19: a systematic review and meta-analysis of observational studies. *Anaesthesia* 2020; 75: 1340-9.
33. Carboni Bisso I, Huespe I, Lockhart C, et al. Clinical characteristics of critically ill patients with COVID-19. *medRxiv* 2020; 2020.12.09.20246413.