

## Clinical characteristics and outcomes of critically ill COVID-19 patients admitted to an Infectious Diseases Intensive Care Unit in Portugal

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### Abstract

**Objective:** We aimed to describe the characteristics and outcomes of patients with coronavirus disease 2019 (COVID-19) admitted to an intensive care unit (ICU) in Portugal.

**Design:** This is an observational retrospective study. Demographic and clinical data were collected. Respiratory failure treated with invasive mechanical ventilation (IMV) and death during ICU stay were the main outcomes evaluated.

**Setting:** This study was conducted in the Infectious Diseases ICU of Centro Hospitalar e Universitário de São João, in Porto, Portugal, between March 11 and August 17, 2020.

**Patients and participants:** All consecutive patients with confirmed Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection, admitted to the ICU during the study period were enrolled, and 62 patients were included.

**Measurements and results:** The median age was 71 years (IQR, 54-78) and 39 (62.9%) were male. Thirty-four (54.8%) patients received

IMV in contrast to 28 (45.2%) who were not intubated and the median lowest PaO<sub>2</sub>/FiO<sub>2</sub> was 86 (IQR, 70-113) in IMV and 150 (94-257) in non-IMV patients. Several patients with severe hypoxemic COVID-19 were treated without IMV, especially with high flow nasal cannula (HFNC). Overall mortality was 21.8% and older age, male sex, active cancer, lower lymphocyte count, higher aspartate aminotransferase (AST) level, and higher creatinine level at admission, hematologic dysfunction, and renal dysfunction during ICU stay were all associated with fatal outcome. Mortality was lower than observed in other series of critically ill patients, although comparisons are limited by different ICU admission criteria, management practices, and duration of follow-up.

**Conclusions:** This study provides data regarding the characteristics and outcomes of COVID-19 critically ill patients that can be used to optimize ICU preparedness in the future.

**Key words:** COVID-19, SARS-CoV-2, critical illness, intensive care, invasive mechanical ventilation.

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### Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged at the end of December 2019 in Wuhan, China, and was identified as a new virus in January 2020. (1) It originated a rapidly spreading illness, coronavirus disease 2019 (COVID-19), affecting thousands of people worldwide. As a consequence, a pandemic was declared on March 11th by the World Health Organization (WHO). (2)

In this context, knowledge has been updated every day. The first case series from China largely included hospitalized patients with severe pneumo-

nia. (3) Further data suggested that approximately 80% of patients were asymptomatic or have mild disease and 20% required hospital admission - approximately a quarter of them in intensive care units (ICU). (4)

COVID-19 is a respiratory disease with variable severity, ranging from mild flu-like syndrome to severe interstitial pneumonia and acute respiratory distress syndrome (ARDS). (5) The disease is described as having a biphasic course, including a first viral response phase, characterized by mild respiratory and constitutional symptoms such as fever, dry cough, and/or malaise, sometimes progressing to viral pneumonia with hypoxemia. (6) Some patients evolve into a host inflammatory response phase, characterized by a cytokine storm and aggressive inflammatory response, implicated in airway damage, respiratory and multi-organ failure, and ARDS. (7,8) Most aged patients or with comorbidities need to be hospitalized for close observation and management, since some of them progress to the most severe stage of the disease, requiring invasive mechanical ventilation (IMV). (9) Sudden decompensation with the need for urgent intubation may happen in patients without respiratory distress at admission. (10)

ICU preparedness is an integral part of any pandemic response worldwide. (11) In Portugal, ICU capacity increased by 23% in the hospitals of the national healthcare system. (12) This study aims to describe the characteristics and outcomes of patients with COVID-19 admitted to an ICU in Portugal, contributing to optimize future responses.

## Materials and methods

In this observational retrospective study, we enrolled consecutively all adult patients ( $\geq 18$  years of age) with laboratory-confirmed SARS-CoV-2 infection, admitted into the Infectious Diseases ICU of Centro Hospitalar e Universitário de São João (CHUSJ), between March 11 and August 17, 2020. A confirmed case of SARS-CoV-2 infection was defined by a positive result on a polymerase chain reaction (PCR) assay of a nasopharyngeal swab. The study was approved by the Ethics Committee of CHUSJ.

Patients' demographic and clinical data were obtained through a review of electronic medical records. These included demographics, previous comorbidities, chronic medication, initial symptoms, laboratory results, oxygen supplementation and IMV parameters, prone positioning, extracorporeal membrane oxygenation (ECMO), organ dysfunctions, bacterial secondary infection, antivirals, antibiotics, and immunomodulating drugs

prescribed. The outcomes of interest were respiratory failure treated with IMV and death during ICU stay, including follow-up for 14 days after ICU discharge. In the group referred to as non-IMV we included patients treated with high flow nasal cannula (HFNC), Venturi-mask oxygen supplementation, and bi-level positive airway pressure (BPAP). Statistical analysis was performed using SPSS software version 26. Descriptive statistics were used to summarize the data, including frequencies and percentages for categorical variables and median and inter-quartile range (IQR) or mean and standard deviation (SD) for numerical variables. The most suitable statistical test was used according to the variable's type and distribution. A  $p$ -value  $< 0.05$  was considered significant.

## Results

Sixty-two patients were included in this study. Patients' demographic and clinical data are summarized in **Table 1**. The median age was 71 years (IQR, 54-78), and 39 (62.9%) were male. Forty-three (69.4%) patients were discharged from the ICU and seven were transferred to other ICUs after intubation for IMV due to the absence of available beds in our unit.

Comorbidities were identified in 58 (93.5%) cases and the most frequent were hypertension (62.9%), diabetes mellitus (37.1%), cardiovascular disease (27.4%), and active cancer (17.7%). Seventeen (27.4%) and 11 (17.7%) patients were previously treated with angiotensin-converting-enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB), respectively.

The median time from symptoms onset to hospital admission was seven days (IQR, 4-11) while to ICU admission was eight days (IQR, 5-14). Fever (77.4%), dyspnoea (56.5%), dry cough (56.5%), and asthenia (33.9%) were the most common initial symptoms. Lymphocytopenia was a common laboratory finding (58.1%) with a median lymphocyte count of 905 per cubic millimetre ( $\text{mm}^3$ ) (IQR, 580-1363). Abnormal liver enzymes were present in 34 patients (54.8%).

The overall median lowest  $\text{PaO}_2/\text{FiO}_2$  was 101 (IQR, 76-163) during ICU stay. Thirty-four (54.8%) patients received IMV in contrast to 28 (45.2%) patients who were not intubated, including 19 (30.7%) treated with HFNC, seven (11.3%) with Venturi-mask oxygen supplementation, and two (3.2%) with BPAP.

Between IMV and non-IMV patients, a higher proportion of male patients was observed in the first group (76.5% vs 46.4%,  $p=0.03$ ). Fever and dyspnoea were more common in IMV compared to

non-IMV patients (88.2% vs 64.3%,  $p=0.052$  and 70.6% vs 39.3%,  $p=0.027$ , respectively). IMV patients had lower median lymphocytes count and higher median aspartate aminotransferase (AST) level compared to non-IMV patients ( $p=0.008$  and  $p=0.06$ , respectively). No other statistically significant differences were seen in age, comorbidities, symptoms, or laboratory results distribution between these groups (**Table 1**).

IMV parameters registered during ICU stay (mean $\pm$ SD), included compliance 38.5 $\pm$ 13.9 millilitres per centimetre of water (ml/cmH<sub>2</sub>O), positive end-expiratory pressure (PEEP) 12.3 $\pm$ 2.2 cmH<sub>2</sub>O, plateau pressure 25.2 $\pm$ 3.9 cmH<sub>2</sub>O, and driving pressure 13.6 $\pm$ 3.6 cmH<sub>2</sub>O. The mean plateau and driving pressure values were higher in IMV patients who died compared to survivors (95% CI 0.897; 7.283,  $p=0.014$  and 95% CI 1.172; 9.264,  $p=0.019$ , respectively). The mean IMV duration was 16 $\pm$ 9.2 days. Twenty (74.1%) patients needed prone positioning and two venovenous ECMO (**Table 2**).

Besides respiratory failure (85.5%), the most common organ dysfunctions were cardiovascular (41.8%), hematologic (25.5%) and renal (22.6%), and 22 (40%) patients had bacterial secondary infection. The median lowest PaO<sub>2</sub>/FiO<sub>2</sub> was 86 (IQR, 70-113) in IMV patients and 150 (IQR, 94-257) in non-IMV patients ( $p=0.001$ ). IMV patients had higher proportion of cardiovascular and hematologic dysfunction (77.8% vs 7.1%,  $p<0.001$  and 40.7% vs 10.7%,  $p=0.025$ , respectively) as well as secondary bacterial infection (74.1% vs 7.1%,  $p<0.001$ ) compared to non-IMV patients. Hydroxychloroquine (HCQ) was given in 23 cases (41.8%) and associated with azithromycin in 15 cases (27.3%), with no documented side effects. Thirteen patients (23.6%) received corticosteroids, two remdesivir, and one tocilizumab (**Table 3**).

The median length of ICU stay was 9 days (IQR, 3-21). Overall mortality was 21.8% (12 patients), including seven (25.9%) IMV patients and five (17.9%) without indication to escalate intensive care due to subjacent condition. Older age ( $p=0.036$ ), male sex ( $p=0.018$ ), and active cancer ( $p=0.008$ ) were more common in patients who died compared to those who survived. Non-survivors had lower median lymphocyte count and higher median creatinine and AST level at admission compared to survivors ( $p=0.005$ ,  $p=0.033$ , and  $p=0.031$ , respectively). A higher proportion of hematologic ( $p=0.007$ ) and renal ( $p=0.024$ ) dysfunction was observed in patients with fatal outcome. No readmissions were registered during the study period. Of note, the outcome of IMV patients

transferred to other ICUs was not included in the mortality estimate.

## Discussion

This study describes the 62 critically ill patients with laboratory-confirmed SARS-CoV-2 infection admitted to an ICU in Portugal. To the best of our knowledge this is the first description of COVID-19 critical illness in Portugal. The main findings include the 54.8% proportion of IMV and 21.8% mortality.

The majority of patients had chronic comorbidities before ICU admission, most frequently hypertension, diabetes mellitus, and cardiovascular disease. However, the proportion of patients with active cancer (11%) was higher than previously described. (13,14) Lymphocytopenia and elevated liver enzymes were frequent laboratory findings at admission.

Respiratory failure was the most common organ failure (85.5%), as suggested by the PaO<sub>2</sub>/FiO<sub>2</sub> ratio of 101 mmHg (IQR 76-163), and IMV was needed in the most severe cases (54.8%). IMV proportion had substantial variation in other series (41.9-87.3%) considering that respiratory failure remained relatively constant. (13-15) This fact reflects different ICU admission criteria and management practices, but also the initial knowledge gap. The pathophysiology of respiratory failure in COVID-19 is not completely understood. Marini, et al suggested a mismatch between hypoxemia and respiratory system compliance and raised questions about the optimal settings of IMV in these patients. (16) The timing to intubate patients and initiate IMV also remains controversial. (17) In our unit, we treated several patients with severe hypoxemia, but not hypercapnia, without IMV, especially with HFNC with good outcomes. However, HFNC should be used under high clinical surveillance, ideally in ICU. (17) We also found that patients who received IMV had high oxygen demand with PEEP and plateau pressure settings comparable to those recommended for classic ARDS. (18,19) These patients needed prolonged mechanical ventilation lasting several days to weeks. These two aspects denote the challenge of IMV in COVID-19 critical illness.

Approximately 40% of patients had cardiovascular dysfunction or shock requiring vasopressors and about 33% had elevated troponin level. In 733 critically ill patients described by Xie, et al, about 60% had evidence of cardiac injury (i.e. elevated troponin level). (13) We were not able to perform routine echocardiogram in all our patients to assess myocardial function and it is still unclear whether

cardiomyopathy reflects direct cardiac injury from SARS-CoV-2 or is a consequence of deregulated inflammatory response. Secondary bacterial infection was described in 40% of patients suggesting that these patients are at increased risk for coinfection that may also explain part of the outcomes observed.

The most commonly used therapy was HCQ, particularly at the beginning of the pandemic. So far, the evidence does not attribute a relevant role to this drug in COVID-19. A recent meta-analysis that included 29 studies did not associate HCQ with reduced mortality. (20) Corticosteroids were also used, as it exists some evidence of their benefit in severe COVID-19 patients. (21)

The first case series of critically ill patients from China (22) and the USA (23,24) reported mortality above 50%. These rates were higher than the critical illness caused by SARS-CoV in China (25) and similar to Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in Saudi Arabia. (26) A lower mortality (14.3% and 33%) has been observed in influenza A (H1N1) critical illness. (27,28) In April, Wang, et al (29) and Grasselli, et al (30) reported substantially lower mortality in ICU (38.7% and 26%, respectively), although 58% of the patients in the latter cohort were still in the ICU at the end of the study. In our study, the overall mortality (21.8%) was lower than observed in the most recent studies from China (13) (58.3%), Italy (15) (53.4%), and the USA (14) (35.4%) but similar to Germany (31) (22%). This fact may be explained by a smaller population-adjusted number of cases and a less overcrowded ICU capacity in our country. (32) Once again, different ICU admission criteria, management practices and duration of follow-up limit these comparisons. Eleven (91.7%) non-survivors were 65 years of age or older and seven (58.3%) had at least 75 years of age. Male sex and active cancer were also associated with fatal outcome in our study. Older age and active cancer are well-established independent risk factors of mortality in critically ill patients with COVID-19, but the relationship between sex and mortality remains controversial. (13-15,31) Gupta, et al showed that kidney and liver dysfunction at ICU admission were independent risk factors for death but not lymphocyte count. (14) In our study low lymphocyte count, high creatinine, and AST levels at admission were all associated with fatal outcome.

Our study has several limitations. First, this is a retrospective study with a small number of patients from a single centre. Second, data regarding the cause of death and cardiac function were not rou-

tinely collected. Finally, due to the small sample size, adjustment for confounders was not performed.

## **Conclusion**

In this case series of COVID-19 critically ill patients admitted to an ICU, 54.8% were intubated and 21.8% died. Several patients with severe hypoxemic COVID-19 were treated without IMV, especially with HFNC. We consider HFNC to be a valid alternative to treat COVID-19 in non-dyspnoeic patients who have hypoxemia but not hypercapnia, thus, avoiding complications associated with intubation and deep sedoanalgesia. However, HFNC should be used under high clinical surveillance, ideally in ICU.

Overall mortality was lower than observed in other series of critically ill patients, although different ICU admission criteria, management practices, and duration of follow-up limit these comparisons. Older age, male sex, and active cancer were associated with fatal outcome, as well as lymphocytopenia, elevated AST, and elevated creatinine at admission, renal dysfunction and hematologic dysfunction during ICU stay.

Although the Portuguese healthcare system ICU capacity did not overload, this continues to be a plausible scenario in the event of a second pandemic wave with a higher number of patients requiring intensive care. This study provides data regarding the characteristics and outcomes of COVID-19 critically ill patients that can be used to optimize ICU preparedness in the future.

## **Contributions**

AM, MM, ASP, and LS designed the study; LS supervised the study. All authors contributed to data collection and analysis. All authors revised the report and approved this version.

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## **Declaration of interests**

None.

## **Ethical statement**

This study was approved by the Ethics Committee of the Centro Hospitalar e Universitário de São João, Porto, Portugal and therefore was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

**Table 1.** Baseline characteristics at presentation to the Intensive Care Unit

	IMV (n=34)	Non-IMV (n=28)	p-value	Survivors (n=43) <sup>a</sup>	Non-survivors (n=12) <sup>a</sup>	p-value	All patients (n=62)
Age (years), median (IQR)	72 (61-77)	70 (43-78)	0.404	67 (45-77)	77 (68-80)	0.036*	71 (54-78)
Male, no. (%)	26 (76.5)	13 (46.4)	0.030*	22 (51.2)	11 (91.7)	0.018*	39 (62.9)
BMI, mean±SD	28.9±4.55	26.6±5.26	0.096	28±5.62	27.4±2.21	0.609	27.9±4.95
Comorbidities, no. (%)							
- Hypertension	22 (64.7)	17 (60.7)	0.952	25 (58.1)	10 (83.3)	0.176	39 (62.9)
- Diabetes mellitus	15 (44.1)	8 (28.6)	0.319	16 (37.2)	6 (50)	0.512	23 (37.1)
- Cardiovascular disease	8 (23.5)	9 (32.1)	0.638	9 (20.9)	6 (50)	0.068	17 (27.4)
- Active cancer	5 (14.7)	6 (21.4)	0.523	5 (11.6)	6 (50)	0.008*	11 (17.7)
- COPD	4 (11.8)	3 (10.7)	1.000	5 (11.6)	2 (16.7)	0.639	7 (11.3)
- Chronic hepatic disease	2 (5.9)	3 (10.7)	0.650	4 (9.3)	0 (0)	0.566	5 (8.1)
- Chronic kidney disease	3 (8.8)	2 (7.1)	1.000	3 (7)	2 (16.7)	0.298	5 (8.1)
Medication, no. (%)							
- ACE inhibitors	10 (29.4)	7 (25)	0.919	10 (23.3)	5 (41.7)	0.274	17 (27.4)
- ARB	4 (11.8)	7 (25)	0.200	10 (23.3)	1 (8.3)	0.422	11 (17.7)
- Immunomodulators	3 (8.8)	2 (7.1)	1.000	4 (9.3)	1 (8.3)	1.000	5 (8.1)
- Corticosteroids	1 (2.9)	3 (10.7)	0.320	4 (9.3)	0 (0)	0.566	4 (6.5)
Symptoms, no. (%)							
- Fever	30 (88.2)	18 (64.3)	0.052**	32 (74.4)	11 (91.7)	0.265	48 (77.4)
- Dyspnoea	24 (70.6)	11 (39.3)	0.027*	23 (53.5)	7 (58.3)	1.000	35 (56.5)
- Dry cough	19 (55.9)	16 (57.1)	1.000	21 (48.8)	8 (66.7)	0.443	35 (56.5)
- Asthenia	14 (41.2)	7 (25)	0.285	15 (34.9)	3 (25)	0.731	21 (33.9)
- Phlegm	13 (38.2)	6 (21.4)	0.249	16 (37.2)	3 (25)	0.511	19 (30.6)
- Diarrhoea	5 (14.7)	6 (21.4)	0.523	9 (20.9)	1 (8.3)	0.430	11 (17.7)
- Dysgeusia/dysosmia	2 (5.9)	3 (10.7)	0.650	5 (11.6)	0 (0)	0.574	5 (8.1)
Time from symptoms onset to ICU admission (days), median (IQR)	8 (5-14)	9 (4-14)	0.952	9 (5-16)	7 (5-13)	0.647	8 (5-14)

Laboratory measures, median (IQR)							
- Lymphocytes (/mm <sup>3</sup> )	765 (493-1083)	1285 (753-1507)	0.008*	1200 (730-1470)	575 (383-905)	0.005*	905 (580-1363)
- Platelets (x10 <sup>9</sup> /l)	147 (113-192)	180 (134-216)	0.101	173 (120-215)	132 (118-156)	0.152	161 (115-209)
- Creatinine (mg/dl)	1.02 (0.73-1.25)	0.75 (0.6-1.22)	0.116	0.76 (0.69-1.22)	1.2 (0.75-2.39)	0.033*	0.91 (0.71-1.25)
- AST (U/l)	48 (38-63)	33 (25-62)	0.060**	38 (26-59)	58 (43-66)	0.031*	44 (32-63)

Legend: IMV=invasive mechanical ventilation; IQR=interquartile range; BMI=body mass index; SD=standard deviation; COPD=chronic obstructive pulmonary disease; ACE=angiotensin converting enzyme; ARB=aldosterone receptor blocker; ICU=intensive care unit; AST=aspartate transaminase; <sup>a</sup>IMV patients transferred to other ICUs were not included (n=7); \*Statistical significance (p<0.05); \*\*Borderline statistical significance.

**Table 2.** Invasive mechanical ventilation during the course of illness in the ICU

	Survivors (n=20) <sup>a</sup>	Non-survivors (n=7) <sup>a</sup>	p-value	All patients (n=27) <sup>a</sup>
IMV parameters, mean±SD				
- Compliance (ml/cmH <sub>2</sub> O)	40.5±15.8	32.6±2.9	0.286	38.5±13.9
- PEEP (cmH <sub>2</sub> O)	12.1±2	13.2±2.7	0.286	12.3±2.2
- Plateau pressure (cmH <sub>2</sub> O)	24±2.9	28.1±4.9	0.014*	25.2±3.9
- Driving pressure (cmH <sub>2</sub> O)	12.2±2	17.4±4.4	0.019*	13.6±3.6
Prone positioning, no. (%)	13 (65)	7 (100)	0.137	20 (74.1)
VV ECMO, no. (%)	1 (5)	1 (14.3)	0.459	2 (7.4)
Time from admission to IMV (days), median (IQR)	2 (1-5)	1 (0-3)	0.534	2 (1-4)
IMV duration (days), mean±SD	16±9	16±10	0.975	16±9.2

Legend: ICU=intensive care unit; IMV=invasive mechanical ventilation; SD=standard deviation; PEEP=positive end-expiratory pressure; VV ECMO=veno-venous extracorporeal membrane oxygenation; IQR=interquartile range; <sup>a</sup>IMV patients transferred to other ICUs were not included (n=7); \*Statistical significance (p<0.05).

**Table 3.** Clinical measures during the course of illness in the ICU

	IMV (n=27) <sup>a</sup>	Non-IMV (n=28) <sup>a</sup>	p-value	Survivors (n=43) <sup>a</sup>	Non-survivors (n=12) <sup>a</sup>	p-value	All patients (n=55) <sup>a</sup>
Organ dysfunctions, no. (%)							
- Respiratory	26 (96.3)	21 (75)	0.051**	35 (81.4)	12 (100)	0.178	47 (85.5)
~ Lowest PaO <sub>2</sub> /FiO <sub>2</sub> , median (IQR)	86 (70-113)	150 (94-257)	0.001*	123 (86-186)	77 (49-96)	0.004*	101 (76-163)
- Cardiovascular	21 (77.8)	2 (7.1)	<0.001*	15 (34.9)	8 (66.7)	0.095	23 (41.8)
~ Troponin I (ng/l), median (IQR)	38.7 (17.1-226)	19.7 (5.9-49)	0.040*	28.7 (8.6-66)	42.4 (23.3-181)	0.331	31.9 (9.4-87)
- Hematologic	11 (40.7)	3 (10.7)	0.025*	7 (16.3)	7 (58.3)	0.007*	14 (25.5)
- Renal	8 (29.6)	5 (17.9)	0.478	7 (16.3)	6 (50)	0.024*	13 (22.6)
- Hepatic	9 (33.3)	3 (10.7)	0.088	8 (18.6)	4 (33.3)	0.429	12 (21.8)
- Neurologic	5 (18.5)	1 (3.6)	0.101	4 (9.3)	2 (16.7)	0.602	6 (10.9)
Secondary bacterial infection, no. (%)	20 (74.1)	2 (7.1)	<0.001*	15 (34.9)	7 (58.3)	0.188	22 (40)
Drug therapies (no. (%))							
- Hydroxychloroquine	11 (40.7)	12 (42.9)	1.000	18 (41.9)	5 (41.7)	1.000	23 (41.8)
+ Azithromycin	8 (29.6)	7 (25)	0.934	10 (23.3)	5 (41.7)	0.274	15 (27.3)
- Corticosteroids	12 (44.4)	1 (3.6)	0.001*	8 (18.6)	5 (41.7)	0.129	13 (23.6)
- Remdesivir	2 (7.4)	0 (0)	0.236	2 (4.7)	0 (0)	1.000	2 (3.6)
- Tocilizumab	1 (3.7)	0 (0)	0.491	0 (0)	1 (8.3)	0.218	1 (1.8)
Length of ICU stay (days), median (IQR)	20 (16-34)	3 (2-6)	<0.001*	9 (3-24)	9 (3-18)	0.892	9 (3-21)

Legend: ICU=intensive care unit; IMV=invasive mechanical ventilation; PaO<sub>2</sub>=arterial oxygen partial pressure; FiO<sub>2</sub>=fractional inspired oxygen; IQR=interquartile range; <sup>a</sup>IMV patients transferred to other ICUs were not included (n=7); \*Statistical significance (p<0.05); \*\*Borderline statistical significance.

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