

Original Article

SARS-CoV-2 in Spanish Intensive Care Units: Early experience with 15-day survival in Vitoria



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ABSTRACT

Purpose: Community transmission of SARS-CoV-2 was detected in Spain in February 2020, with 216% intensive care unit (ICU) capacity expanded in Vitoria by March 18th, 2020.

Methods: We identified patients from the two public hospitals in Vitoria who were admitted to ICU with confirmed infection by SARS-CoV-2. Data reported here were available in April 6th, 2020. Mortality was assessed in those who completed 15-days of ICU stay.

Results: We identified 48 patients (27 males) with confirmed SARS-CoV-2. Median [interquartile range (IQR)] age of patients was 63 [51–75] years. Symptoms began a median of 7 [5–12] days before ICU admission. The most common comorbidities identified were obesity (48%), arterial hypertension (44%) and chronic lung disease (37%). All patients were admitted by hypoxemic respiratory failure and none received non-invasive mechanical ventilation. Forty-five (94%) underwent intubation, 3 (6%) high flow nasal therapy (HFNT), 1 (2%) extracorporeal membrane oxygenation (ECMO) and 22 (46%) required prone position. After 15 days, 14/45 (31%) intubated patients died (13% within one week), 10/45 (22%) were extubated, and 21/45 (47%) underwent mechanical ventilation. Six patients had documented super-infection. Procalcitonin plasma above 0.5 µg/L was associated with 16% vs. 19% ($p = 0.78$) risk of death after 7 days.

Conclusion: This early experience with SARS-CoV-2 in Spain suggests that a strategy of right oxygenation avoiding non-invasive mechanical ventilation was life-saving. Seven-day mortality in SARS-CoV-2 requiring intubation was lower than 15%, with 80% of patients still requiring mechanical ventilation. After 15 days of ICU admission, half of patients remained intubated, whereas one third died.

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1. Introduction

Since the initial identification of SARS-CoV-2 infections in Wuhan, it has been important to identify characteristics beyond China with implications in management [1,2]. Reports describing

intensive care unit (ICU) patients with SARS-CoV-2 out of China are still limited [3,4]. The clinical course of adult inpatients in Wuhan has been reported [5] with a high mortality rate and a risk of death above 90% in presence of high (0.05 µg/L) procalcitonin (PCT) plasma [5]. Because most patients in China and Italy received non-invasive ventilation (NIV), information is needed on patients following a strategy of early intubation without inducing potential ventilator-induced lung injury. Moreover, in view of the limitation of resources, it is also important to improve insight on 7-day mortality and identify different phenotypes for personalised

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management [6]. In Vitoria (capital of Alava), a city in the Basque Country that experienced the acceleration curve before other Spanish provinces (in relation to a massive contagion in a funeral) with 216% ICU capacity being already effective on March 18th, 2020 (see comparison with Madrid (89%), Barcelona (17%) and other provinces in Fig. 1), anticipating the effect in other regions.

This present study aimed at reporting the epidemiology of the first patients admitted with SARS-CoV-2 in Spanish ICUs, twenty days after the first admission in a hospital located at ground zero (Fig. 1) in Spain. Secondary objectives were: to compare with the first ICU admissions during the 2009 influenza pandemic in Spain and the first reported series of ICU patients with SARS-Cov-2 in Wuhan and USA. Because of mortality reports in Wuhan [5] suggesting a close association, we assessed correlation between PCT plasma at ICU admission and 7-day mortality.

2. Methods

2.1. Study design

All consecutive SARS-CoV-2 adult patients (≥ 18 years old) from the University Hospital Araba (Vitoria, Spain) between March 4th, 2020 and March 31th, 2020 were included. All patients that required hospitalisation with a COVID-19 diagnosis according to WHO interim guidance [7] were included. Patients were followed until ICU discharge or death from March 4th, 2020 (first patient admission) to March 31th, 2020. All clinical data were collected prospectively by the investigators. PCT plasma levels samples were obtained within 24 ICU admissions.

Non-invasive ventilation was not indicated in this cohort. Intubation was clinically indicated in presence of respiratory alkalosis with progressive hyperventilation when delivering high oxygen concentrations.

2.2. Data collection

Basic epidemiological, clinical, laboratory, microbiology, treatment, and outcome data were extracted (HB) and standardised in a CRF, modified from the ISARIC CRF. The study protocol was approved by the IRB and informed consent was waived (ref. 2020-022). Patient data were censored at 15 days of follow up, on April 6th, 2020 and survival data were estimated at 7-day and 15-day after ICU admission.

2.3. Laboratory procedures

Clinical specimens for SARS-CoV-2 identification were obtained in accordance with Centres of Disease Control guidelines. Methods for laboratory confirmation of SARS-CoV-2 polymerase chain reaction (PCR) were performed at the hospital laboratory.

2.4. Definitions

A confirmed case was defined by a positive result on a reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay of a nasopharyngeal swab or respiratory specimen. Comorbidities were identified from hospital charts. Definitions used in this article have been reported elsewhere [8].

2.5. Biomarkers measurement

Procalcitonin plasma levels were determined with the Assay Alinity I[®], Abbott, EEUU. The assay has a detection limit of 0.02 $\mu\text{g/L}$ with a probability of 95%, sensitivity of 0.06 $\mu\text{g/L}$ (upper-reference-range 0.5 $\mu\text{g/L}$ in healthy subjects). Determination of PCT plasma levels was performed within 24 hours after ICU admission.

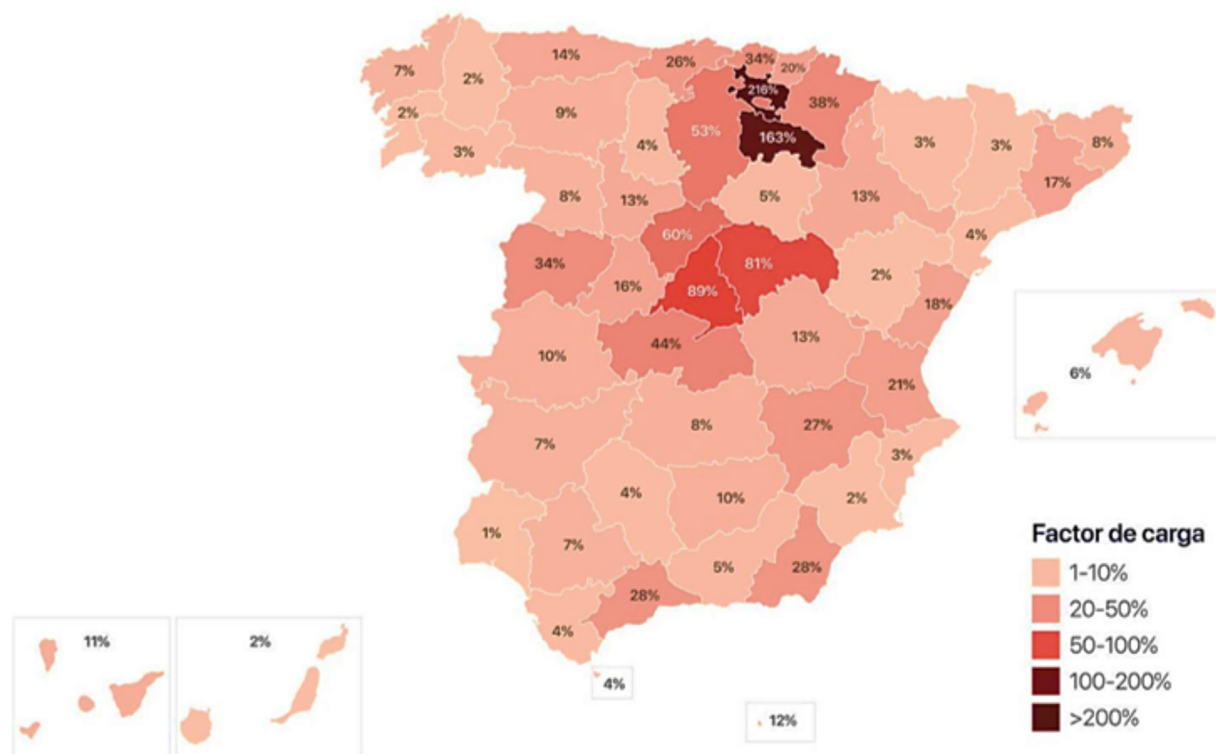


Fig. 1. Percentages of ICU beds occupied on March 18th, 2020 in Spain.

Table 1

Baseline characteristics of the population with confirmed SARS-CoV-2, compared with series in Seattle (Arentz et al.), Wuhan (Yang et al.) and pandemic 2009 influenza in Spain (Rello et al.).

Study	Current study Spain	Arentz et al., 2020 USA [13]	Yang et al., 2020 China [11]	Rello et al., 2009 Spain [4]
Illness	SARS-CoV-2 pneumonia	SARS-CoV-2 pneumonia	SARS-CoV-2 pneumonia	Influenza A (H1N1)
Total patients with confirmed illness	48	21	52	32
Age, mean (SD or range)	63 (12)	70 (43–92)	60 (13)	40 (14)
Sex				
Male	27 (56%)	11 (52%)	35 (67%)	21 (66%)
Female	21 (44%)	10 (48%)	17 (33%)	11 (34%)
Days from onset symptoms to ICU admission, median (IQR)	7 (5–12)	–	10 (7–13)	3 (2–6)
APACHE II score, mean (SD)	15 (5)	–	17 (1)	14 (6)
SOFA score, mean (SD)	7 (3)	–	–	7 (3)
Signs and symptoms ^a				
Fever	48 (100%)	11 (52%)	51 (98%)	706 (96%)
Cough	35 (74%)	11 (48%)	40 (77%)	647 (88%)
Dyspnoea	42 (88%)	–	33 (63%)	–
Malaise	21 (44%)	–	18 (35%)	221 (30%)
Myalgia	2 (4%)	–	6 (12%)	508 (69%)
Headache	–	–	3 (6%)	434 (59%)
Rhinorrhea	–	–	3 (6%)	–
Vomiting	–	–	2 (4%)	–
Arthralgia	–	–	1 (2%)	–
Chest pain	–	–	1 (2%)	–
Sore throat	–	–	–	427 (58%)
Sudden onset symptoms	–	–	–	338 (46%)
Shortness of breath	–	17 (76%)	–	–
Treatment				
Antibacterial agents	42 (88%)	–	49 (94%)	32 (100%)
beta-lactams plus fluoroquinolones	–	–	–	20 (63%)
beta-lactams plus macrolides	–	–	–	6 (19%)
beta-lactams plus linezolid	–	–	–	5 (16%)
levofloxacin	17 (35%)	–	–	1 (3%)
ceftriaxone	22 (46%)	–	–	–
azithromycin	10 (21%)	–	–	–
linezolid	9 (19%)	–	–	–
other beta-lactams	15 (31%)	–	–	–
Antiviral agents	45 (94%)	–	23 (44%)	21 (66%)
Oseltamivir standard dose (75 mg bid)	–	–	18 (35%)	32 (100%)
Oseltamivir high dose (150 mg bid)	–	–	–	10 (31%)
Ganciclovir	–	–	14 (27%)	–
Lopinavir	–	–	7 (14%)	–
Kaletra	45 (94%)	–	–	–
Others				
Steroids	17 (35%)	–	30 (58%)	11 (34%)
Immunoglobulin	–	–	28 (54%)	–
Tocilizumab	2 (4%)	–	–	–
Chloroquine	45 (94%)	–	–	–
Interferon	41 (85%)	–	–	–
Vasoconstrictor agents	–	14 (67%)	18 (35%)	20 (63%)
Renal replacement therapy	–	–	9 (17%)	7 (22%)
Prone position ventilation	–	8 (50%)	6 (12%)	8 (33%)
MV	45 (94%)	15 (71%)	37 (71%)	24 (75%)
Invasive	–	–	22 (42%)	16 (67%)
Non-invasive	–	–	29 (56%)	8 (33%)
HFNC	–	–	33 (64%)	–
ECMO	1 (2%)	–	6 (12%)	–
Comorbidities/Complications				
Obesity	23 (48%)	–	–	10 (31%)
BMI 30 to 40	15 (31%)	–	–	6 (19%)
BMI > 40	7 (15%)	–	–	4 (13%)
Arterial hypertension	21 (44%)	–	–	1 (3%)
Hyperglycaemia	–	–	18 (35%)	–
Acute kidney injury	–	–	15 (29%)	–
Liver dysfunction	–	–	15 (29%)	–
Cardiac injury	–	–	12 (23%)	–
HAP	–	–	7 (13%)	–
Gastrointestinal haemorrhage	–	–	2 (4%)	–
Pneumothorax	–	–	1 (2%)	–
Bacteremia	–	–	1 (2%)	–
Urinary tract infection	–	–	1 (2%)	–
Diabetes mellitus	9 (19%)	7 (33%)	–	–
Smoker	9 (19%)	–	–	1 (3%)
Hypothyroidism	9 (19%)	–	–	–
Heart disease	5 (10%)	–	–	–
Immunosuppression	3 (6%)	3 (14%)	–	1 (3%)
Asthma	–	2 (9%)	–	–

Table 1 (Continued)

Study	Current study Spain	Arentz et al., 2020 USA [13]	Yang et al., 2020 China [11]	Rello et al., 2009 Spain [4]
COPD	18 (38%)	7 (33%)	–	5 (16%)
Pregnancy	–	–	–	4 (13%)
Chronic renal failure	–	–	–	2 (6%)
HIV	–	–	–	1 (3%)
Neuromuscular disease	–	–	–	1 (3%)
Haematologic disease	–	–	–	1 (3%)
Congestive heart failure	–	9 (43%)	–	1 (3%)
Rheumatologic disease	–	1 (5%)	–	–
Obstructive sleep apnoea	–	6 (29%)	–	–
Chronic kidney disease	–	10 (48%)	–	–
History of solid organ transplant	1 (2%)	2 (10%)	–	–
Cirrhosis	–	1 (5%)	–	–
ARDS	48 (100%)	20 (95%)	35 (67%)	–
Pathogens identified				
<i>Pseudomonas aeruginosa</i>	3 (6%)	–	1 (2%)	3 (9%)
<i>Aspergillus flavus</i>	–	–	1 (2%)	1 (3%)
<i>Aspergillus fumigatus</i>	–	–	1 (2%)	–
<i>Klebsiella pneumoniae</i>	–	–	1 (2%)	–
<i>Serratia marcescens</i>	–	–	1 (2%)	–
Invasive candidiasis	–	–	1 (2%)	–
<i>Enterococcus faecium</i>	1 (2%)	–	–	–
<i>Haemophilus influenzae</i>	1 (2%)	–	–	–
MRSA	1 (2%)	–	–	–
Mortality at 28-days	16 (36%)	11 (52%)	32 (62%)	16 (50%)
Length of MV for survivors, median (IQR)	–	–	–	10 (1–21)

APACHE: acute physiology and chronic health evaluation II; ARDS: acute respiratory distress syndrome; BMI: body mass index; COPD: chronic obstructive pulmonary disease; ECMO: Extracorporeal membrane oxygenation; HAP: hospital-acquired pneumonia; HIV: positive human immunodeficiency virus; HFNC: High-flow nasal cannula; ICU: intensive care unit; IMV: invasive mechanical ventilation; IQR: interquartile range; MRSA: Methicillin-resistant *Staphylococcus aureus*; MV: mechanical ventilation; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SD: standard deviation; SOFA: sequential organ failure assessment.

^a Rello et al., reported signs and symptoms from a total of 735 cases of influenza A (H1N1) were confirmed in Spain in 2009.

2.6. Statistical analysis

Considering the rapid spread of the COVID-19 pandemic, the aim of the study was to report a fast overview of the situation in one of the first cities to be impacted by the outbreak. Therefore, no sample size was calculated.

Continuous variables were described as medians with interquartile range (IQR) or mean with standard deviation (SD), and categorical variables were presented as counts and percentages. Pairwise comparisons for categorical variables were performed by using the Pearson's χ^2 test. Comparisons between continuous variables used Student's *t*-test and Mann–Whitney test according to their distribution. Statistical significance was considered if the *P*-value was less than 0.05. Statistical analyses were performed with SPSS Statistics version 25.0 software (IBM).

Association between survival and PCT plasma levels was estimated using Kaplan–Meier curves. Hazard ratios (HR) and 95% confidence intervals (CI) were computed using the long rank test. Statistical significance was considered if the *P*-value was less than 0.01. Statistical analyses were performed with GraphPad prism 6 software.

3. Results

From March 4th to March 24th, 2020, 48 patients with laboratory-confirmed COVID-19 infection (median age 63 years [51–75], 27 males, no pregnant women) were admitted and included. No patients were admitted from a nursing home. Patient characteristics are shown in Table 1. Obesity (48%), arterial hypertension (44%) and chronic lung disease (38%) were the three most associated comorbidities, whereas diabetes mellitus, hypothyroidism and history of tobacco use were reported in 19% of admissions.

The median time to onset of symptoms prior to ICU admission was 7 days [5–12 days] (Table 1). The most common symptoms at ICU admission were fever (100%), dyspnoea (88%), cough (73%) and malaise (44%). Myalgias (4%) were very uncommon. Ninety-four percent of patients received antiviral treatment with lopinavir/ritonavir and hydroxychloroquine, plus interferon beta (85%). Empirical antibiotic agents were administered to 42 patients, whereas super-infection was identified in 6 patients.

All patients were admitted with hypoxemic respiratory failure and none received non-invasive mechanical ventilation. Forty-five (94%) underwent intubation and 3 (6%) high-flow oxygen nasal therapy (HFNT). Tracheostomy was performed in five (11%) ventilated patients. Prone position was performed in 22 patients (49% of mechanically ventilated patients) and none received inhaled nitric oxide or prostacyclin. One patient was transferred to a referral centre for veno-venous extracorporeal membrane oxygenation (ECMO) therapy. One myocarditis was documented. A flow chart (Fig. 2) is detailing outcomes on day-7 post intubation. Outcomes for individual patients are summarised in Fig. 3.

After 7 days of ICU admission, among 45 intubated patients, six (13%) died, one (2%) underwent ECMO and one (2%) was extubated. Among 45 intubated, 37 (82%) still underwent mechanical ventilation. After 15 days, 14 (31%) intubated patients died (77% above 65 years), 21 (47%) remained with mechanical ventilation and 10 (22%) were extubated. Thirteen (27%) of the 48 patients admitted to the ICU were discharged alive.

Six patients had super-infection documented, with median PCT plasma levels 0.2 $\mu\text{g/L}$ [0.1–2.9] vs. 0.4 $\mu\text{g/L}$ [0.1–1.5] in non-infected ones ($p = 0.22$). PCT plasma levels details with different breakpoints are showed in Table 2. PCT plasma levels above 0.5 $\mu\text{g/L}$ were 16% vs. 19.0% ($p > 0.20$) for survivors and non-survivors, respectively. PCT plasma levels details are showed in Fig. 4 and 5. No significant differences were identified, using a breakpoint of 1 $\mu\text{g/L}$ (Table 2 and Figs. 4 and 5). A Kaplan–Meier survival curve

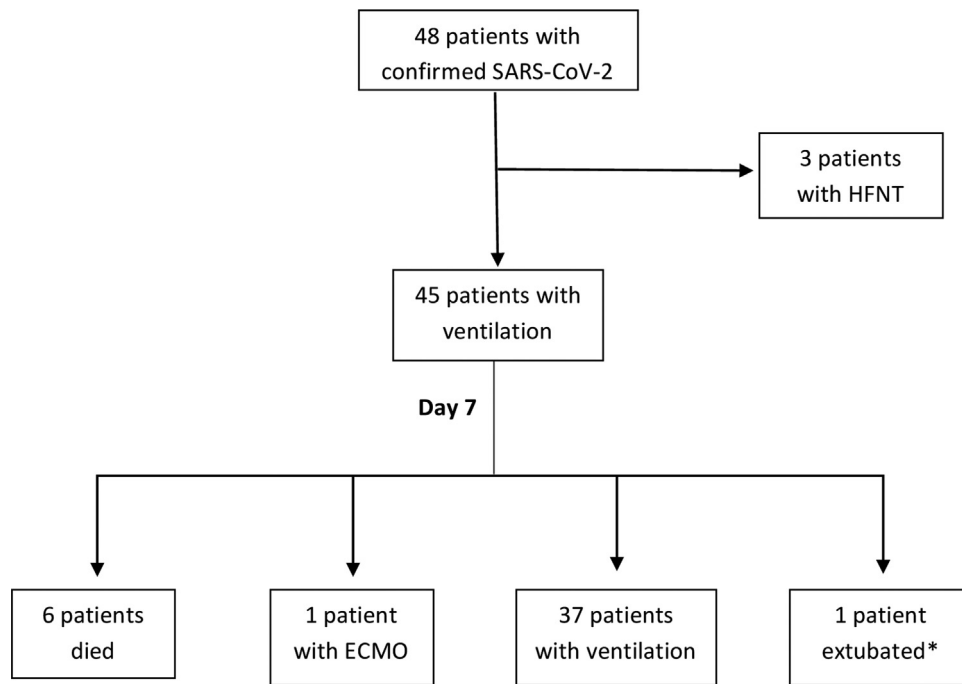


Fig. 2. Flowchart of detailing outcomes at day-7 post ICU admission.

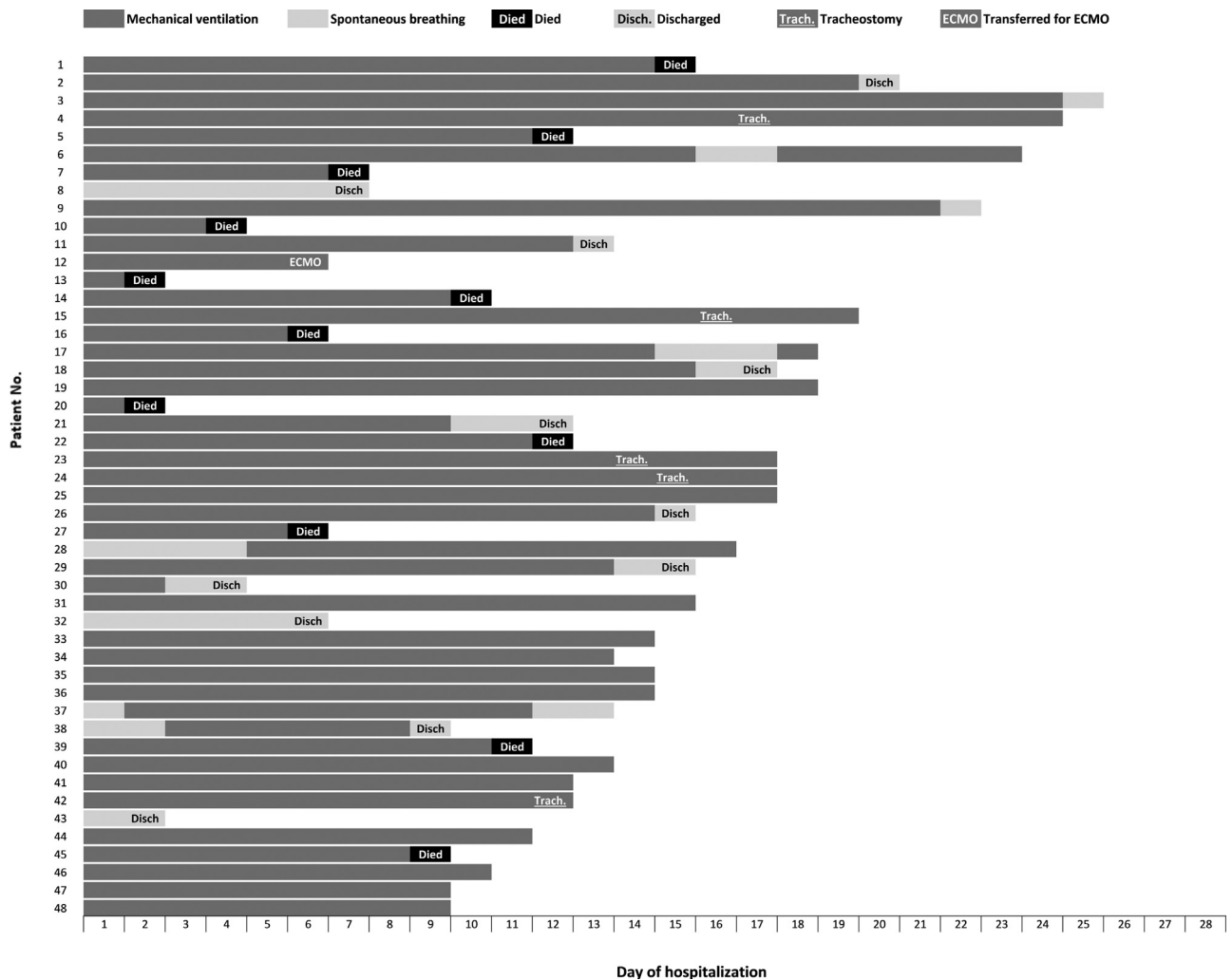


Fig. 3. Outcomes for individual patients included in the manuscript (assessed April 6th, 2020).

Table 2

PCT plasma levels at different breakpoints of the population with confirmed SARS-CoV-2 pneumonia.

	All	≤0.5 PCT µg/L	>0.5 PCT µg/L	≤1 PCT µg/L	>1 PCT µg/L
Total patients with confirmed illness	48 ^a	25 (52%)	21 (44%)	32 (67%)	14 (30%)
Age, median (IQR)	67 (53–74)	65 (51–75)	68 (54–73)	66 (52–74)	67 (54–73)
Sex					
Male	27 (56%)	11 (44%)	14 (67%)	17 (53%)	8 (57%)
Female	21 (44%)	14 (56%)	7 (33%)	15 (47%)	6 (43%)
Days from onset symptoms to ICU admission, median (IQR)	7 (5–12)	7 (5–13)	8 (6–12)	7 (5–13)	8 (5–13)
APACHE II score, median (IQR)	15 (12–19)	15 (13–18)	17 (12–19)	15 (12–19)	17 (12–18)
SOFA score, median (IQR)	7 (4–8)	6 (4–8)	7 (4–11)	6 (3–8)	8 (4–11)
Signs and symptoms					
Fever	48 (100%)	25 (100%)	21 (100%)	32 (100%)	14 (100%)
Cough	35 (73%)	20 (80%)	14 (67%)	24 (75%)	10 (71%)
Dyspnoea	42 (88%)	23 (92%)	18 (86%)	30 (94%)	11 (79%)
Malaise	21 (44%)	8 (32%)	11 (52%)	12 (38%)	7 (50%)
Myalgia	2 (4%)	1 (4%)	1 (5%)	2 (6%)	–
Treatment					
Antibacterial agents	42 (88%)	20 (80%)	20 (95%)	27 (84%)	13 (93%)
levofloxacin	17 (35%)	4 (16%)	12 (57%)	8 (25%)	8 (57%)
ceftriaxone	22 (46%)	9 (36%)	11 (52%)	14 (44%)	6 (43%)
azithromycin	10 (21%)	4 (16%)	5 (24%)	6 (19%)	3 (21%)
linezolid	9 (19%)	7 (28%)	2 (10%)	7 (22%)	2 (14%)
other beta-lactams	15 (31%)	11 (44%)	4 (19%)	11 (35%)	4 (29%)
Others					
Kaletra	45 (94%)	25 (100%)	19 (90.5%)	31 (97%)	13 (92.9%)
Steroids	17 (35%)	11 (44%)	6 (28.6%)	12 (38%)	5 (36%)
Tocilizumab	2 (4%)	2 (8%)	–	2 (6%)	–
Chloroquine	45 (94%)	25 (100%)	19 (90.5%)	31 (97%)	13 (93%)
Interferon	41 (85%)	24 (96%)	16 (76.2%)	29 (91%)	11 (79%)
MV	45 (94%)	23 (92%)	20 (95.2%)	30 (94%)	13 (93%)
ECMO	1 (2%)	1 (4%)	–	1 (3%)	–
Comorbidities					
Obesity	23 (48%)	12 (48%)	10 (48%)	16 (50%)	6 (43%)
BMI 30 to 40	15 (31%)	9 (36%)	6 (28%)	11 (34%)	3 (21%)
BMI > 40	7 (15%)	3 (12%)	4 (19%)	4 (13%)	3 (21%)
Arterial hypertension ^b	21 (44%)	7 (28%)	13 (62%)	11 (34%)	9 (64%)
Lung disease	18 (37%)	9 (36%)	8 (38%)	11 (34%)	6 (43%)
Smoker	9 (19%)	5 (20%)	4 (19%)	7 (22%)	2 (14%)
Heart disease	5 (10%)	2 (8%)	3 (14%)	3 (9%)	6 (43%)
Diabetes mellitus	9 (19%)	3 (12%)	5 (24%)	4 (13%)	4 (28%)
Hypothyroidism	9 (19%)	6 (24%)	3 (14%)	6 (19%)	3 (21%)
Immunosuppression	3 (6%)	2 (8%)	1 (5%)	3 (10%)	–
Pathogens identified					
<i>Pseudomonas aeruginosa</i>	3 (6%)	3 (12%)	–	3 (9%)	–
<i>E. faecium</i>	1 (2%)	–	1 (5%)	1 (3%)	–
<i>H. influenza</i>	1 (2%)	–	1 (5%)	–	1 (7%)
MRSA	1 (2%)	1 (4%)	–	1 (3%)	–
Mortality at 3-days	3 (6%)	1 (4%)	2 (9%)	2 (6%)	1 (7%)
Mortality at 7-days	6 (15%)	2 (8%)	4 (19%)	4 (12.5%)	2 (14.2%)

APACHE: acute physiology and chronic health evaluation II; BMI: body mass index; ECMO: Extracorporeal membrane oxygenation; ICU: intensive care unit; IMV: invasive mechanical ventilation; IQR: interquartile range; MRSA: Methicillin-resistant *Staphylococcus aureus*; MV: mechanical ventilation; NR: not reported; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SD: standard deviation; SOFA: sequential organ failure assessment

^a Only forty-seven patients had PCT value.

^b $P < 0.05$ for breakpoint PCT at 0.5 and $P = 0.06$ for breakpoint PCT at 1.

(Fig. 6) is detailing overall survival rates and correlations with initial PCT plasma (P -value = 0.22).

4. Discussion

This study describes 48 critically ill patients with COVID-19 and severe acute respiratory failure in Vitoria, Spain, from March 4th, 2020 to March 31th, 2020. Patients received HFNT or intubation, but non-invasive mechanical ventilation was not applied. Two weeks after ICU admission, three out of ten intubated patients have died, and half of the patient cohort required prolonged ventilatory support. Two out of ten intubated patients were extubated (and discharged), most at the second week of ventilation. PCT plasma levels (threshold 0.5 µg/L) failed to predict mortality. Our findings suggest that an oxygenation strategy emphasising optimisation of

oxygenation, intubation based on clinical criteria of hyperventilation and avoiding ventilator-induced lung injury associated with non-invasive mechanical ventilation would be life-saving in a significant proportion of patients.

Table 1 compares current findings with first series of SARS-CoV2 in the ICU in China, USA, and 2009 pandemic influenza in Spain. Clinical presentation is consistent with a recent systematic review [9], lymphocytopenia and coagulation alterations being common at hospital admission, with some important differences documented when compared with pandemic influenza in 2009 (Table 1), as reported elsewhere [2], and also with the first ICU series reported from Wuhan [10]. Obesity was the most common comorbidity in our report, suggesting differences in western countries regarding Wuhan reports (11), followed by hypertension and chronic respiratory diseases. The low prevalence of immuno-

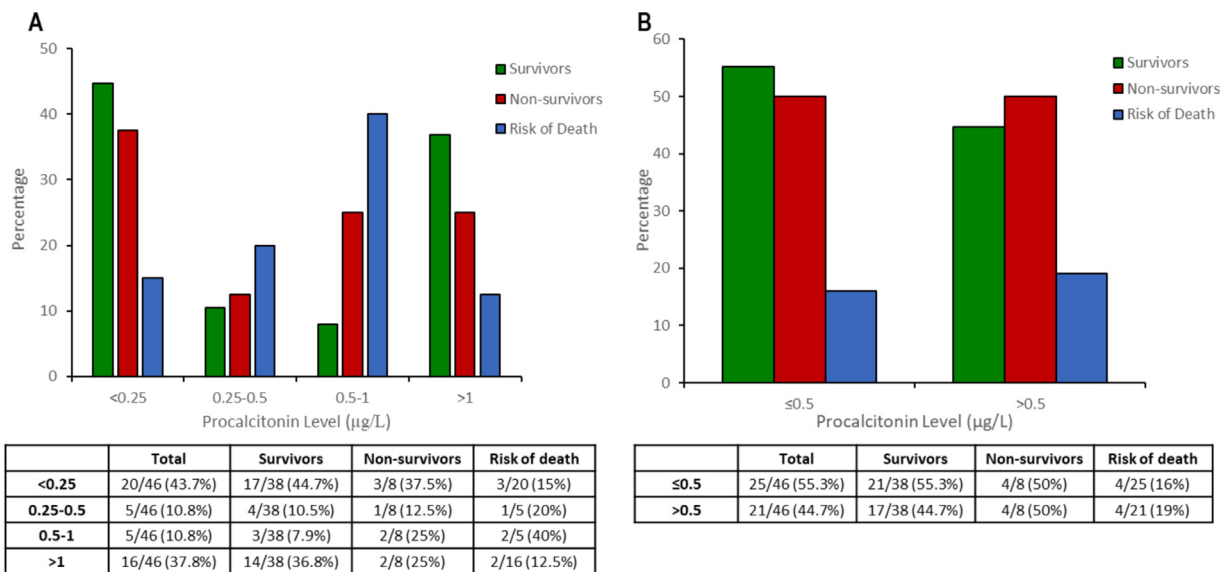


Fig. 4. Patients distribution with SARS-CoV-2 pneumonia according to survivors or non-survivors by PCT levels (A) four breakpoints of PCT levels (B) breakpoint of PCT level at 0.5.

compromised (solid organ transplants or HIV) and pregnant women compared with severe influenza-infected patients may be associated with the interaction of coronavirus with innate immunity. Fei Zhou et al. [5] reported a risk of death above 90% in patients with high procalcitonin, which is not consistent with our findings. This can be due to different laboratory techniques, super-infection rates or degree of acute lung injury (no NIV was applied in our cohort). Although more information on PCT is required [12], our findings suggest that no prognostic information can be inferred. The earliest extubation occurred three days after initiation of mechanical ventilation, but nine subsequent patients were extubated within the next week (Fig. 3). These figures may be different depending of SARS-CoV-2 phenotype, prior strategy of oxygenation (HFNT, continuous positive airway pressure (CPAP) or NIV), and strategies of management post-ventilation (levels of positive end-expiratory pressure (PEEP), use of inhaled nitric oxide, etc). Further research is required to identify how to improve management. Most patients were admitted to the ICU after a few days of fever above 38.5 °C, arriving at the emergency department (ED) severely dehydrated and hyperventilating. Hypovolaemia leads to increased dead space and pulmonary hypoperfusion, needing to be corrected. High PEEP and furosemide may lead to unnecessary requirement of vasopressors and induce acute kidney injury, and thus in need of continuous veno-venous haemofiltration program (CVVHF).

This early report of characteristics of SARS-CoV-2 influenza in Spain is of interest, as most information currently available is coming from large cohorts in China, or short case series from Italy or USA [5,6,11,13]. An important characteristic is that in the current cohort, no patients were exposed to prior NIV, which was commonly performed using a facial mask in Wuhan or a helmet in Italy, with a protocol of earlier intubation based on hyperventilation unable to maintain SatvO_2 above 90%. Patients in this cohort were intubated a median of 7 days after onset, which is later than in pandemic influenza but earlier than in Wuhan. Zhou et al. [5] reported 97% mortality in intubated patients during a median time (IQR) of 18.5 (15 to 19) days. Seven-day mortality was estimated to be lower than 15% in our cohort and 10 patients were extubated within the second week, which means that the prognosis is better with different strategies of oxygenation. In contrast with reports from China or Seattle suggesting a severe acute respiratory distress syndrome (ARDS), a strategy of early intubation disclosed that

SARS-CoV-2 does not lead to a typical ARDS. In our experience, two thirds of our patients have initial lung compliance ≥ 40 ml/cm H₂O post intubation being consistent with a preliminary report with 16 patients by Gattinoni et al. [6], suggesting that ARDS is a consequence of acute lung injury associated with delayed intubation or super-infection. Thus, NIV seems not recommended and early high PEEP (above 10 cm H₂O is probably not the right ventilatory strategy) may be harmful. Our experience suggests avoiding spontaneous ventilation early in the ED or ward may be harmful. Thus, SARS-CoV-2 patients can be maintained with high-flow oxygen nasal therapy (HFNT) or high-concentration oxygen reservoir if they do not present extreme hyperventilation. Early on this disease, non-intubated patients may benefit from prone position before intubation. Three of our patients were managed like this without intubation and were discharged early. Recruitment manoeuvres should be contraindicated and the benefit of prone position in intubated patients and protective ventilation should be restricted to those developing acute lung injury. These findings suggest that hypoxemic vasoconstriction is the main early mechanism and patients can benefit of inhaled prostacyclin or nitric oxide (before developing tachyphylaxis).

Lastly, although we did not document pulmonary embolisms in our cohort (autopsies were not allowed), laboratory tests are consistent with endothelial injury and micro-thrombosis. Zhou et al. [5] reported serum ferritin with a median above 1400 ng/L among 54 non-survivors in a context of hyperinflammatory states. These patients should receive sCD25 measurements and a bone marrow aspirate to rule out systemic haemophagocytic lymphocytosis, which should be treated with 500 mg/kg gamma globulins/day and dexamethasone 10 mg/12 h for 4 days. The same authors also reported D-dimer above 1 $\mu\text{g/ml}$ among 81% of non-survivors and our findings are consistent with these observations. Although no difference on overall 28-day mortality was found between heparin users and non-users (30.3% vs. 29.7%, $p = 0.91$) in a report among 449 patients with severe SARS-CoV-2 infection in China [14], the 28-day mortality was significantly reduced in those receiving low molecular weight heparin with a D-dimer > 6 fold the upper limit of normal (32% vs. 52%, $P = 0.01$) or a Sepsis-Induced Coagulopathy (SIC) score [15] ≥ 4 (40% vs. 64%, $P = 0.02$).

Our study has several limitations. More than half of the cohort remained in the ICU at the time of censoring on April 6th, 2020 and further outcomes assessment have to be performed. Our sample

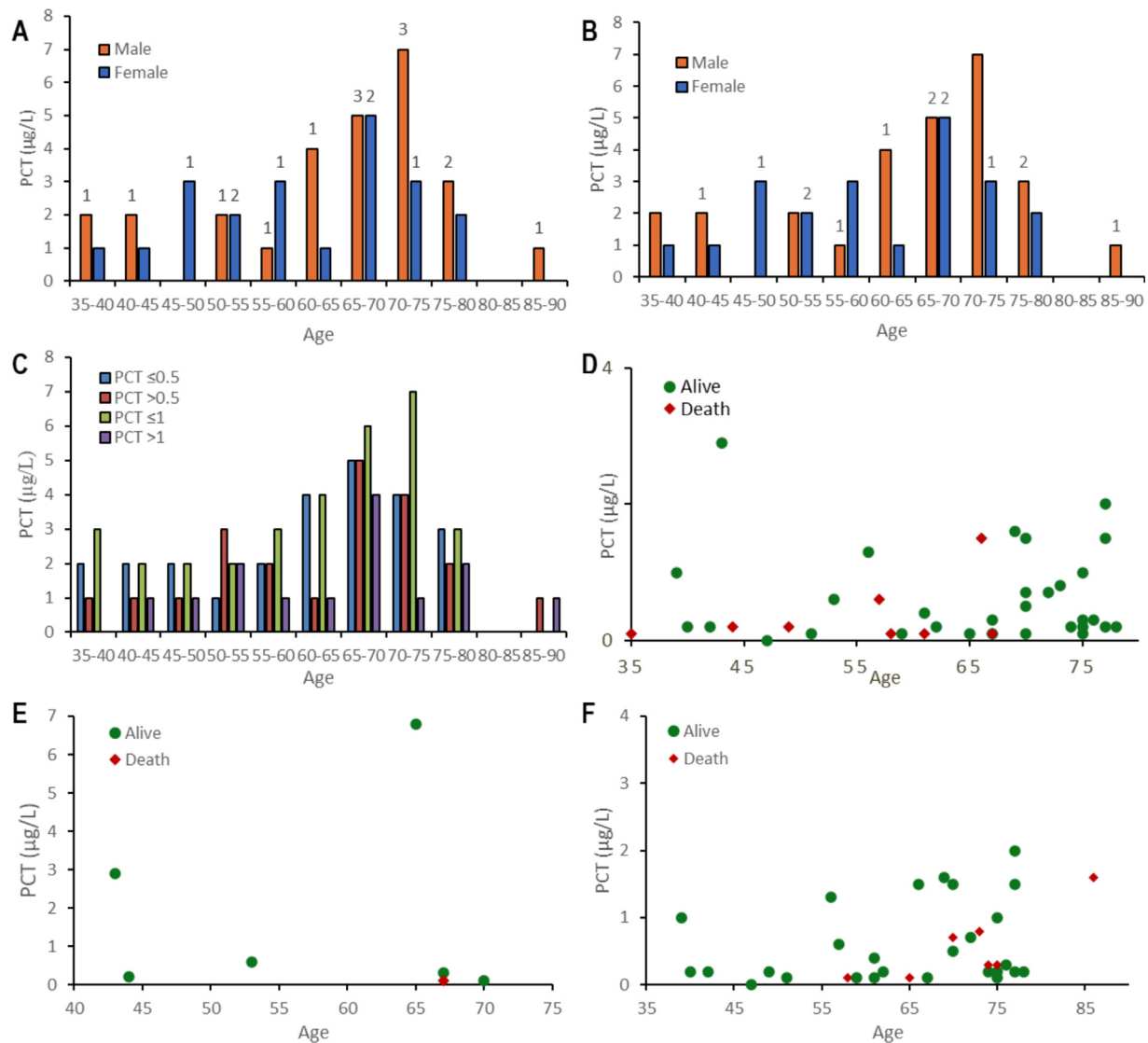


Fig. 5. Patients' distribution with SARS-CoV-2 pneumonia by PCT plasma levels and age: (A) by sex and PCT $\mu\text{g/L} > 0.5$; (B) by sex and PCT $\mu\text{g/L} > 1$; (C) by PCT $\mu\text{g/L} \leq 0.5$ vs. > 0.5 and ≤ 1 vs. > 1 ; (D) Alive and death by PCT $\mu\text{g/L}$; (E) Alive and death by PCT of patients with super-infection; (F) Alive and death by PCT of patients without super-infection. In figures A and B, the numbers indicate the total patients with positive PCT.

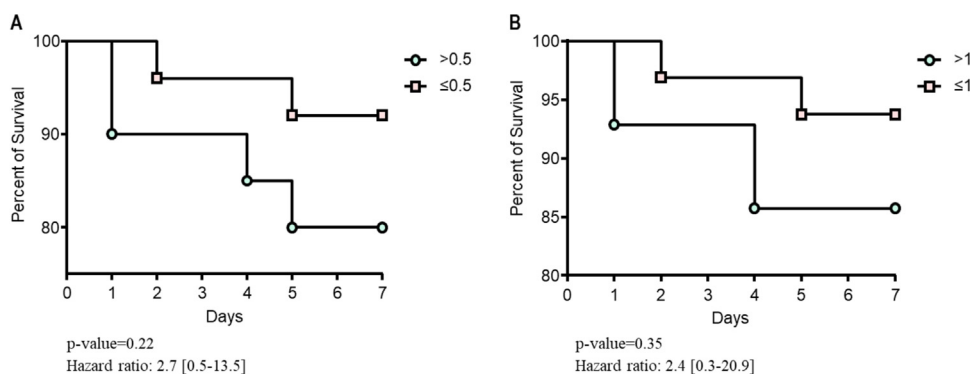


Fig. 6. Kaplan-Meier with 95% confidence interval (CI) representing mortality at 7 days based on PCT values. (A) PCT breakpoint at 0.5; (B) PCT breakpoint at 1. HFNT: High-flow nasal therapy; ECMO: extracorporeal membrane oxygenation.

size is small, because we focused on critically ill, and data cannot be extrapolated to patients hospitalised in medical wards. However, it is an early report illustrative of the epidemiology in South Europe, which can be compared with Wuhan and initial reports of pandemic influenza A H1N1pdm 2009 in Spain (Table 1). We already expanded the ICU capacity above two-fold in March 18th and data cannot be generalisable to patients with another acceleration phase or with different available resources, but may serve to develop contingency plans in other geographical regions. Procalcitonin technique of determination may influence values and data may not be comparable when using other methods, such as KRIPTOR[®] to determine plasma values. Similarly, the strategy of early intubation, without prior NIV trial would mean that data cannot be extrapolated to sites with other management strategies. Lastly, pulmonary compliance and driving pressure was not recorded in the study protocol, limiting identification of phenotypes and extrapolation to other sites.

5. Conclusion

This early experience with SARS-CoV-2 in Spain suggests that the right oxygenation is life-saving. Seven-day mortality in SARS-CoV-2 requiring intubation was lower than 15%, with 80% of patients still requiring prolonged mechanical ventilation. PCT plasma levels do not predict survival. After 15 days of ICU admission, half of patients remained intubated, whereas one third were non-survivors. Our clinical observations provide useful insights that can help to improve management and outcomes.

Disclosure of interest

The authors declare that they have no competing interest.

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Compliance with ethical standards

The study was approved by the Clinical Research Ethics Committee of Araba Hospital (2020-0022) and consent was waived due to the observational nature of the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to privacy (patients' data) but are available from the corresponding author on reasonable request.

Authors' contributions

The study was designed by JR. HB enrolled patients and it is responsible for the integrity of data. An analysis of data was

performed by ST, HB and JM. JR and ST wrote the first draft of the manuscript. All authors contributed scientifically in the subsequent versions. All authors read and approved the final manuscript.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.accpm.2020.04.001>.

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